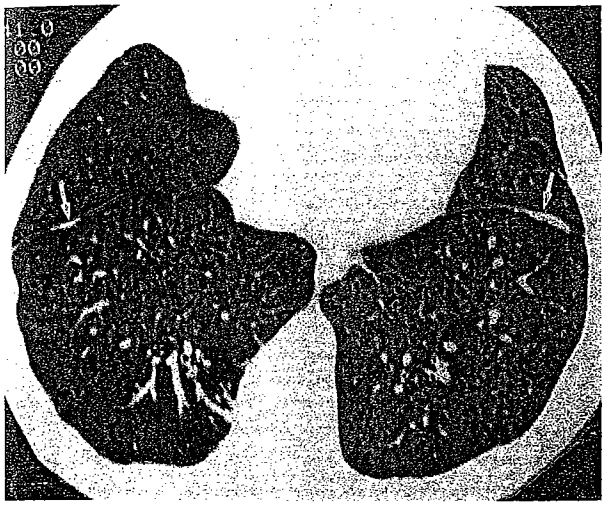

**Figure 60–42. Plaques within Interlobar Fissures.** An HRCT scan demonstrates pleural plaques in the right and left major fissures *(arrows)*. Also noted are curvilinear opacities in the right paravertebral region extending to an area of pleural thickening. The patient was a 71-year-old man who had previously worked in a shipyard.

in the paravertebral regions because the intercostal muscles do not pass internally to the ribs or vertebrae and because the pleura and endothoracic fascia are not thick enough to be seen in these locations. Therefore, any distinct stripe of soft tissue attenuation internal to a rib or in the paravertebral region is abnormal.[645]

In one study of 30 patients in whom conventional and oblique radiographs revealed pleural shadows of uncertain origin, CT demonstrated that the opacities were the result of subpleural fat accumulation in 14 (47%);[644] of the remaining 16 patients, 10 had definite pleural plaques, 4 had no evidence of either plaques or fat, and 2 demonstrated shadows that could not be attributed with certainty to either plaques or fat.

### Calcification

Although noncalcified pleural plaques are the most common radiographic manifestation of asbestos-related disease, they are clearly more striking when calcified (Fig. 60–43). The frequency of calcification is quite variable, ranging from 0% to 50% in different series;[449, 623, 625, 646] these differences in prevalence are probably related to differences in the type of inhaled asbestos. As might be expected, the complication is seen more commonly on CT than on the radiograph. In a study of 100 asbestos-exposed American workers, it was detected on chest radiography in 13, on conventional CT in 16, and on HRCT in 20.[628]

Calcified plaques vary from small linear or circular shadows to shadows that completely encircle the lower portion of the lungs.[647] When calcification is minimal, a radiograph overexposed at maximal inspiration facilitates visibility.[648] The most common site is the diaphragm, although it may be seen at any location.[649] The complication generally does not develop until at least 20 years after the first exposure to asbestos,[624, 649] although the occupational exposure can be relatively short; for example, two patients have been described in whom isolated calcified diaphragmatic plaques developed approximately 20 years after occupational exposure of only 8 and 11 months.[650]

### Diffuse Pleural Thickening

In contrast to a pleural plaque, diffuse thickening is manifested as a generalized, more or less uniform increase in pleural width. Although the term is not precisely defined in the 1980 ILO classification, diffuse pleural thickening is generally considered to be present radiologically when there is a smooth uninterrupted pleural density extending over at least one fourth of the chest wall with or without obliteration of the costophrenic angles.[651] It is diagnosed on CT when a continuous area of pleural thickening greater than 3 mm extends for more than 8 cm craniocaudally and 5 cm around the perimeter of the hemithorax.[652]

On HRCT, the margin between an area of diffuse pleural thickening and the adjacent lung is frequently irregular as a result of parenchymal fibrosis, in contrast to the usually sharply circumscribed margins of pleural plaques.[653] The abnormality is usually associated with contralateral pleural abnormalities, either diffuse pleural thickening or plaques.[654, 655] Although calcification may be present, it is seldom extensive.[655, 656] As with other causes of fibrothorax, asbestos-related pleural thickening seldom involves the mediastinal pleura (although it frequently affects the parietal pleura abutting the paravertebral gutters [Fig. 60–44]).[655, 657] The absence of involvement of the mediastinal pleura can be readily assessed at CT and is often helpful in distinguishing benign from malignant pleural thickening; for example, in one study of 19 patients, only 1 of 8 who had fibrothorax had thickening of the mediastinal pleura as compared with 8 of 11 who had mesothelioma.[655]

### Pleural Effusion

Asbestos-associated pleural effusion is often not appreciated (Fig. 60–45).[658–660] The most comprehensive report of its prevalence and incidence was a study of 1,135 exposed workers and 717 control subjects in which benign asbestos effusion was defined by[660] (1) a history of exposure to asbestos; (2) confirmation of the presence of effusion by radiographs, thoracentesis, or both; (3) absence of other disease related to pleural effusion; and (4) absence of malignant tumor within 3 years. According to these criteria, 34 benign effusions (3%) were identified in the exposed workers compared to none in the control subjects. The likelihood of the presence of effusion was dose related. The latency period was shorter than for other asbestos-related disorders, being the most common abnormality during the first 20 years after exposure. Most effusions were small, 28% recurred, and 66% were unassociated with symptoms.

The major differential diagnoses are tuberculosis and mesothelioma. Of 12 patients in one series, mesothelioma was recognized in one patient 9 years after the first documented effusion.[658] Of four patients in another series, two eventually developed mesothelioma.[661] Differentiation from a tuberculous effusion can be made with confidence only if biopsy and culture specimens are negative. The subject of asbestos-related effusion is discussed in greater detail on page 2754.

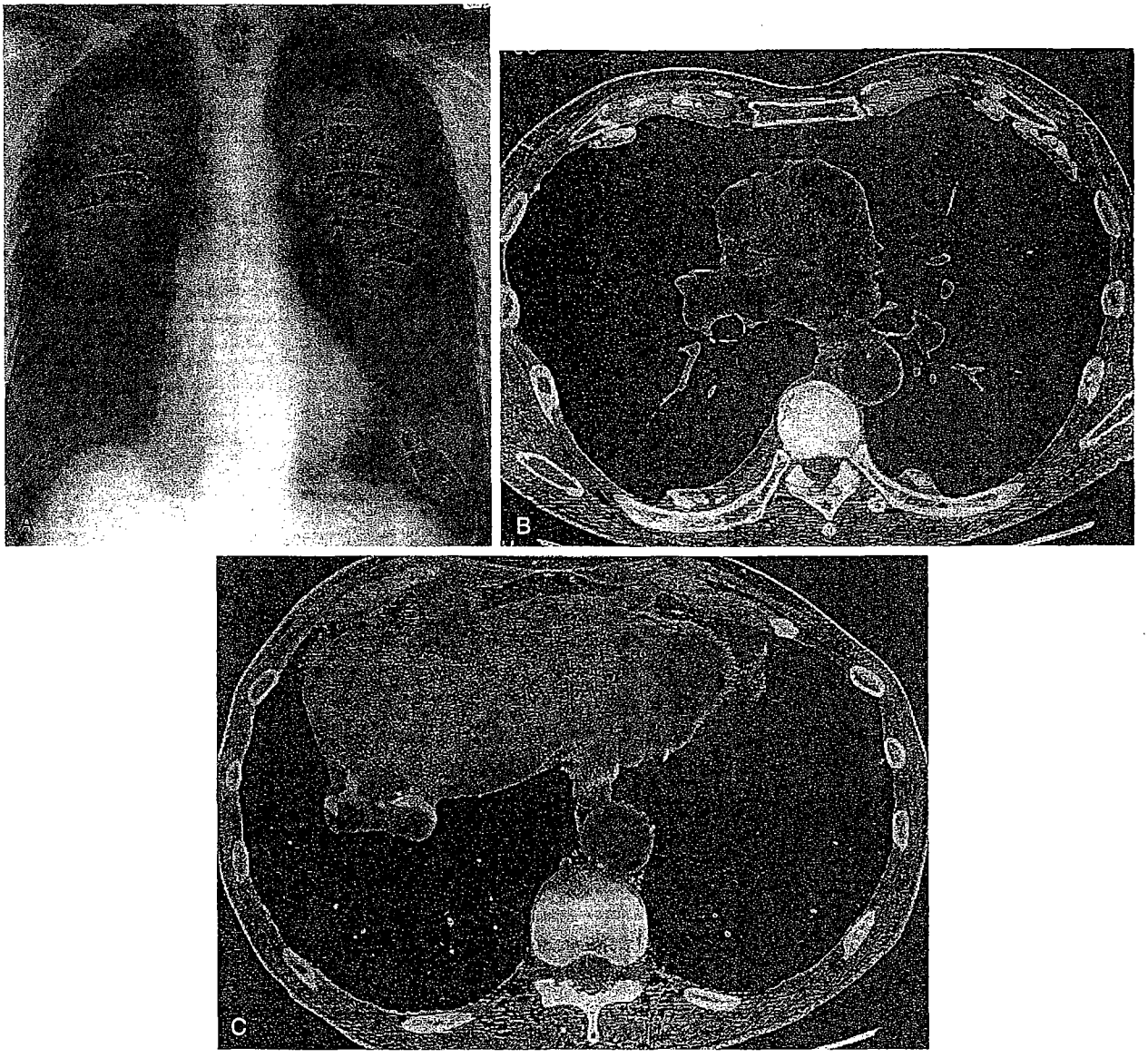


**Figure 60–43. Calcified Pleural Plaques.** A posteroanterior chest radiograph *(A)* in an 82-year-old man demonstrates numerous bilateral calcified pleural plaques. The patient had worked for many years in a shipyard. HRCT *(B* and *C)* demonstrates calcified plaques along the posteromedial and anterolateral chest wall and right hemidiaphragm.

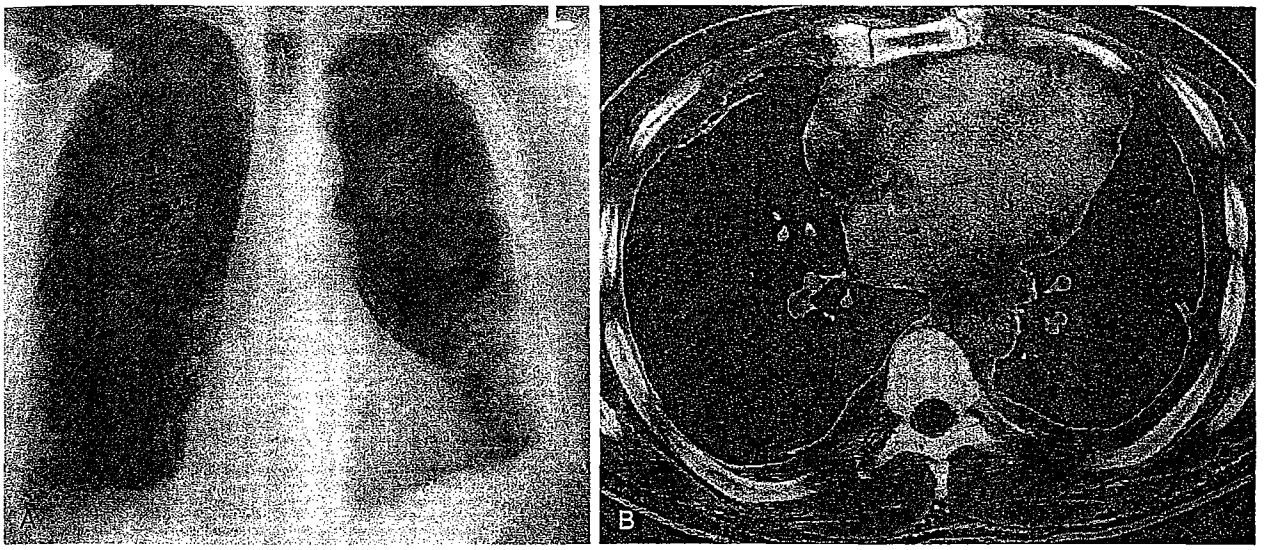


**Figure 60–44. Diffuse Asbestos-Related Pleural Thickening.** A 47-year-old cement worker presented with progressive shortness of breath. A posteroanterior chest radiograph *(A)* demonstrates diffuse bilateral pleural thickening as well as blunting of the costophrenic sulci. Curvilinear opacities extending to the thickened pleura are present in the left lung. An HRCT scan *(B)* confirms the presence of marked pleural thickening. The inner margin of the thickened pleura is irregular because of areas of fibrosis or atelectasis in the adjacent lung. Despite the extensive pleural thickening in the paravertebral portion of the pleura and lateral chest wall, there is no evidence of involvement of the mediastinal pleura.

### Mesothelioma

The most characteristic radiologic manifestation of mesothelioma consists of diffuse pleural thickening (pleural rind) with associated loss of volume of the ipsilateral hemithorax (Fig. 60–46) (*see* also page 2820).[662–666] Pleural effusion is frequently present and is characteristically not associated with contralateral shift of the mediastinum because of the restrictive action of the pleural tumor. Occasionally, the thickening is focal and simulates a pleural plaque.[665, 666] Features that favor mesothelioma include nodular pleural thickening, mediastinal pleural thickening, involvement of the interlobar fissures, and presence of pleural effusion.[655, 657, 665, 666] Pleural plaques are identified on CT in about 30% to 70% of patients who have mesothelioma and pleural calcification in 20% to 50%.[655, 665, 666] The latter is almost invariably within pleural plaques and only rarely within the tumor itself.[667, 668]

In the vast majority of cases, mesothelioma can be readily distinguished from benign asbestos-related pleural plaques on the radiograph and on CT. It may be more difficult, however, to distinguish the tumor from diffuse asbestos-related pleural thickening or other causes of benign or malignant pleural disease.[655, 657] In one review of the CT findings in 74 consecutive patients who had diffuse pleural disease, of whom 39 had malignant disease and 35 benign, features that were most suggestive of malignant disease included circumferential pleural thickening, nodular pleural thickening, parietal pleural thickening of more than 1 cm, and mediastinal pleural involvement (Fig. 60–47).[655] The sensitivities of these findings in detecting malignant pleural involvement were 41%, 51%, 36%, and 56%, with specificities ranging from 88% to 100%; 28 of the 39 malignant cases (sensitivity 72%, specificity 83%) were identified correctly by the presence of one or more of these criteria.

## *Pulmonary Manifestations*

### Asbestosis

Asbestosis is typically manifested on the chest radiograph by the presence of irregular small linear opacities (Fig. 60–48). The development of these abnormalities may be divided into three stages:[669] (1) an early stage of fine reticulation occupying predominantly the lower lung zones and associated with a ground-glass appearance that is probably the result of both pleural thickening and interstitial fibrosis; (2) a stage in which irregular small opacities become more marked, creating a prominent interstitial reticulation; during this stage, the combination of parenchymal and pleural abnormalities leads to partial obscuration of the heart border—the so-called shaggy heart sign—and of the diaphragm; and (3) a late stage in which reticulation becomes visible in the midlung and upper lung zones and the cardiac and diaphragmatic contours become more obscured.[175, 669]

Hilar lymph node enlargement is seldom if ever evident on the radiograph;[648] however, mediastinal lymph nodes greater than 1 cm in diameter are frequently seen on CT.[670] Although asbestosis characteristically exhibits considerable mid- and lower zonal predominance, a small number of patients have been reported in whom slowly progressive pleural and parenchymal fibrosis occurred in the lung apices.[671] Large opacities measuring 1 cm or more in diameter have also been described in occasional patients who have asbestosis;[672] however, these patients have also been exposed to quartz, and it is likely that the latter was responsible for the conglomerate shadows.

Although the radiographic findings of asbestosis are not specific, the diagnosis should be strongly suspected when irregular linear opacities are associated with pleural plaques or diffuse pleural thickening. In approximately 20% of patients who have radiographic findings of asbestosis, however,

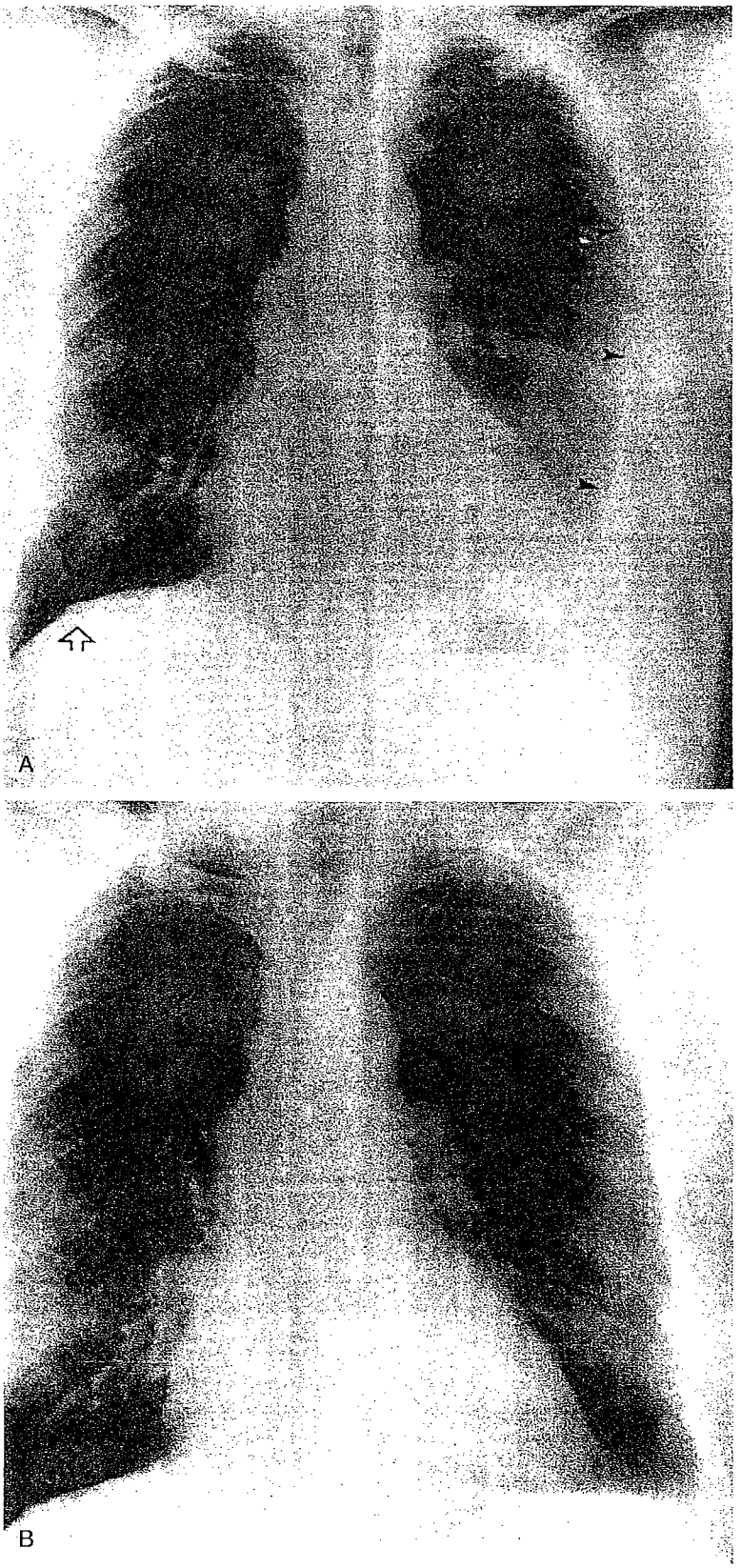


**Figure 60–45. Asbestos-Induced Pleural Effusion, Plaque Formation, and Round Atelectasis.** A posteroanterior chest radiograph *(A)* shows a left pleural effusion of moderate size *(arrowheads)*. A small plaque *(open arrow)* is present on the right hemidiaphragm. A vague opacity is visible behind the right atrial shadow. A posteroanterior radiograph taken 6 months later *(B)* reveals regression of the pleural effusion, although there is residual pleural fibrosis.

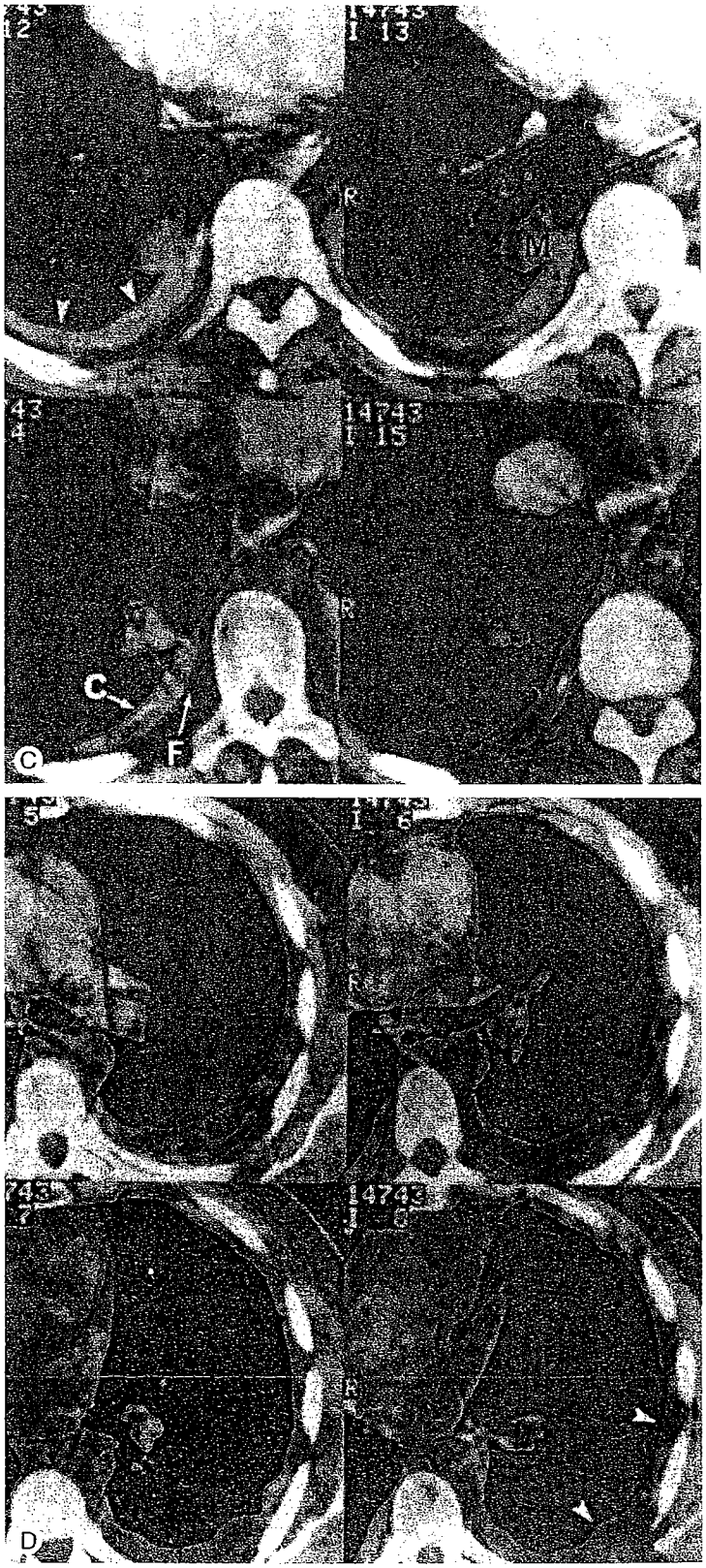


**Figure 60–45** *Continued.* Contiguous 10-mm-thick CT scans (obtained on the same day as the radiograph in *B)* through the right *(C)* and left *(D)* lower lobes demonstrate extensive bilateral posteromedial pleural thickening *(arrowheads).* Note the linear calcifications (C) and increased fat (F) in relation to the thickened pleura on the right. A mass (M) is present adjacent to the thickened pleura.

*Illustration continued on following page*

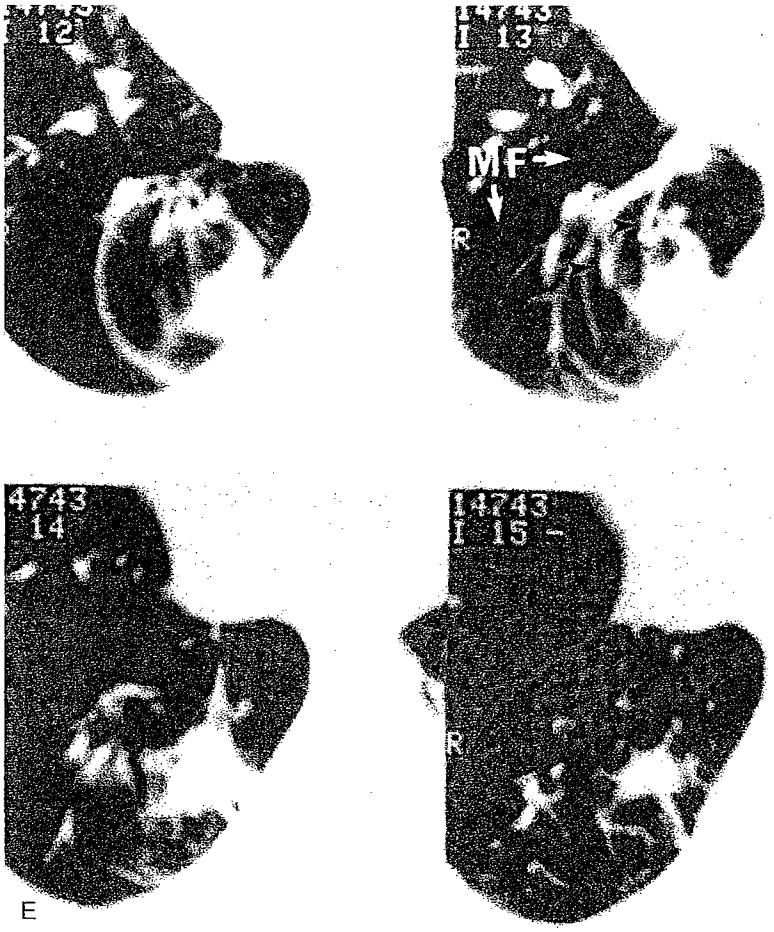


**Figure 60–45** *Continued.* CT scans with lung window technique *(E)* through the mass demonstrate the typical features of round atelectasis: Note the curvilinear displacement of the nearby bronchovascular bundles (*comet tail* sign) *(arrowheads)*. The major fissure (MF) is displaced posteromedially, indicting loss of volume of the right lower lobe. The patient was a 55-year-old man.

there is no radiographic evidence of asbestos pleural disease.[673] Moreover, radiographs fail to demonstrate any parenchymal abnormalities in 10% to 20% of patients who have pathologically proven asbestosis.[674, 675]

As with other conditions, CT—particularly HRCT—allows detection of parenchymal abnormalities not evident on the chest radiograph.[627–629, 663] In one prospective study of 100 asbestos-exposed workers, HRCT findings suggestive of asbestosis were present in 43 of 45 (96%) workers who satisfied clinical criteria of asbestosis, compared to 35 (78%) individuals who had radiographic abnormalities.[628] Another investigation of 60 asbestos workers demonstrated characteristic features of asbestosis in 100% of patients examined by HRCT, compared to 90% for chest radiography.[627] In a review of the HRCT findings and pulmonary function tests in 169 asbestos-exposed workers who had normal chest radiographs (ILO profusion score < 1/0), CT abnormalities consistent with asbestosis were found in 57;[629] this group of patients had significantly lower vital capacity and DLCO than the workers who had normal CT scans.

The most common HRCT manifestations of asbestosis are intralobular linear opacities, irregular thickening of interlobular septa, subpleural curvilinear opacities, subpleural small rounded or branching opacities, and parenchymal bands.[627, 628, 676, 677] Small, round (dotlike), and branching subpleural opacities are considered to be the earliest manifestation of disease.[676] These are typically visible a few millimeters from the pleural surface in a centrilobular distribution. HRCT-pathologic correlation has shown the opacities to reflect the presence of peribronchiolar fibrosis.[676] Subpleural curvilinear opacities are linear areas of increased attenuation of variable length located within 1 cm of the pleura and parallel to the inner chest wall (Fig. 60–49).[677] The majority measure between 5 and 10 cm in length. They are seen most commonly in early disease, although they may reflect honeycombing; they may also represent atelectasis adjacent to pleural plaques.[656, 676, 678]

Another common HRCT feature seen in asbestos-exposed workers is the presence of parenchymal bands, defined as linear opacities measuring 2 to 5 cm in length coursing through the lung, usually to abut an area of pleural thickening.[628] Pathologic correlation has shown these bands to correspond to fibrosis along the bronchovascular sheath or interlobular septa with associated distortion of parenchymal architecture.[678] The bands are more common in asbestosis than in other causes of pulmonary fibrosis; for example, in one study, they were present in 79% of patients who had asbestosis compared with 11% of patients who had idiopathic pulmonary fibrosis.[679] As in other causes of interstitial pulmonary fibrosis, architectural distortion of the secondary lobules and irregular thickening of the interlobular septa are commonly seen in asbestosis (Fig. 60–50). With progression

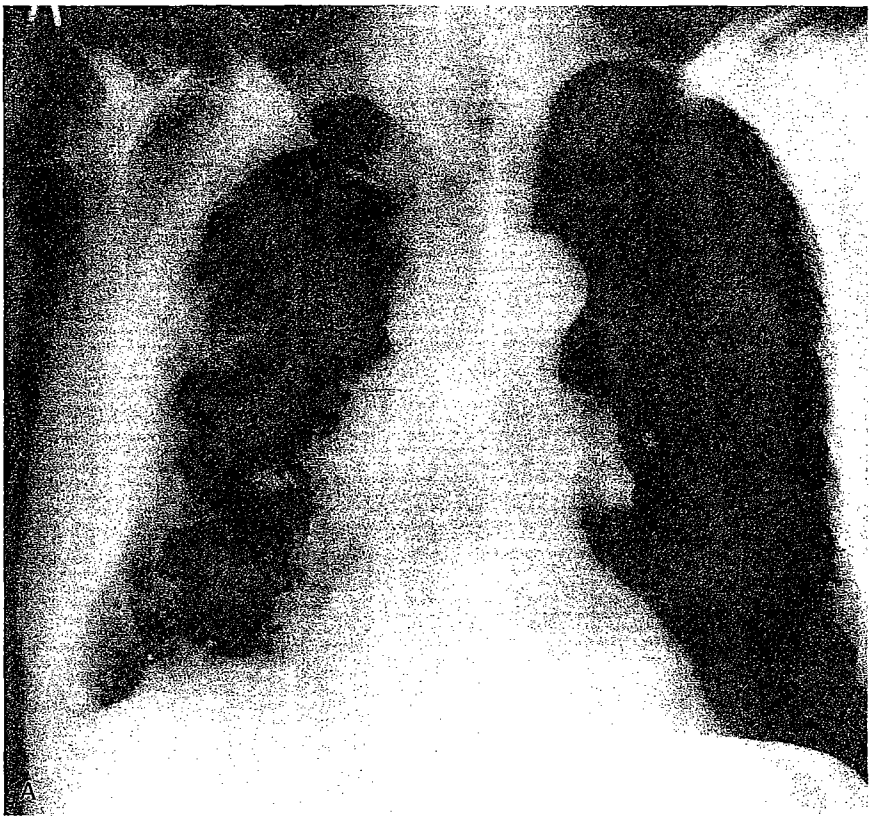

**Figure 60–46. Diffuse Mesothelioma.** An overpenetrated posteroanterior chest radiograph *(A)* shows a reduction in volume of the right hemithorax. There is marked thickening of the pleura over the whole of the right lung, including its mediastinal surface. The thickening is nodular and is associated with a large pleural-based mass in the upper axillary region.

*Illustration continued on following page*

of fibrosis, irregular linear opacities and honeycombing predominate (Fig. 60–51).[630, 680] At all stages, the abnormalities involve predominantly the subpleural regions of the lower lung zones.[654, 678, 680]

These HRCT findings, similar to those on the radiograph, are nonspecific, and no single sign can be considered diagnostic of asbestosis.[681] The likelihood of asbestos-related interstitial fibrosis, however, increases with the number of abnormalities identified.[630] The accuracy of HRCT in predicting the presence of asbestosis was assessed in a group of 24 patients and 6 lungs obtained at autopsy;[630] histologic evidence of asbestosis was present in 25 of the 30 patients or lungs. The most common HRCT findings consisted of intralobular lines or thickened interlobular septa, parenchymal bands, architectural distortion of the secondary lobules, subpleural lines, and honeycombing. To confidently identify the cases as asbestosis, three of these abnormalities had to be identified on CT; although a positive interpretation based on one or two abnormalities increased the sensitivity, it resulted in a substantial decrease in specificity. The procedure was considered to identify insufficient abnormalities to diagnose asbestosis in 5 of the 25 (20%) cases, whereas 10 radiographs (40%) were nondiagnostic.

Because the abnormalities in patients who have mild asbestosis are often limited to the posterior aspects of the lower lung zones, it is recommended that CT scans in these patients be obtained in both supine and prone positions or only in the prone position.[628, 630, 682] Scans with the patient prone are important to distinguish the normal increased opacity in the dependent lung regions from mild fibrosis. In fact, it has been shown that taking a small number of prone images at selected levels in the lower lung zones has a high sensitivity in the detection of asbestos-related pulmonary and pleural abnormalities.[682] This procedure, combined with low radiation dose scans, may become a cost-effective method of screening for asbestosis in high-risk populations.[682, 683]

Gallium-67 lung scans have been shown to be positive in patients who have asbestosis and in sheep exposed to asbestos, a feature possibly attributable to increased transepithelial leakage of serum proteins bound to the isotope as well as to its uptake by intra-alveolar macrophages.[716] Increased epithelial protein permeability, as assessed by DTPA scanning, has also been demonstrated in individuals who have asbestosis.[488, 717]

### Round Atelectasis

The characteristic radiologic manifestation of round atelectasis is a rounded or oval, pleural-based opacity associated with loss of volume and with curving of adjacent pulmonary vessels and bronchi (the comet-tail sign).[684, 685] The opacity typically abuts an area of pleural thickening or a pleural effusion. The comet-tail sign of pulmonary vessels and bronchi as they are swept around and into the focus of atelectasis is easier to identify on CT than on the radiograph (Fig. 60–52). The abnormality may occur anywhere in the lungs but is most commonly found in the posterior aspect of the lower lobes.[686–689] It may be unilateral or bilateral (Fig. 60–53) and may measure from 2 to 7 cm in diameter.

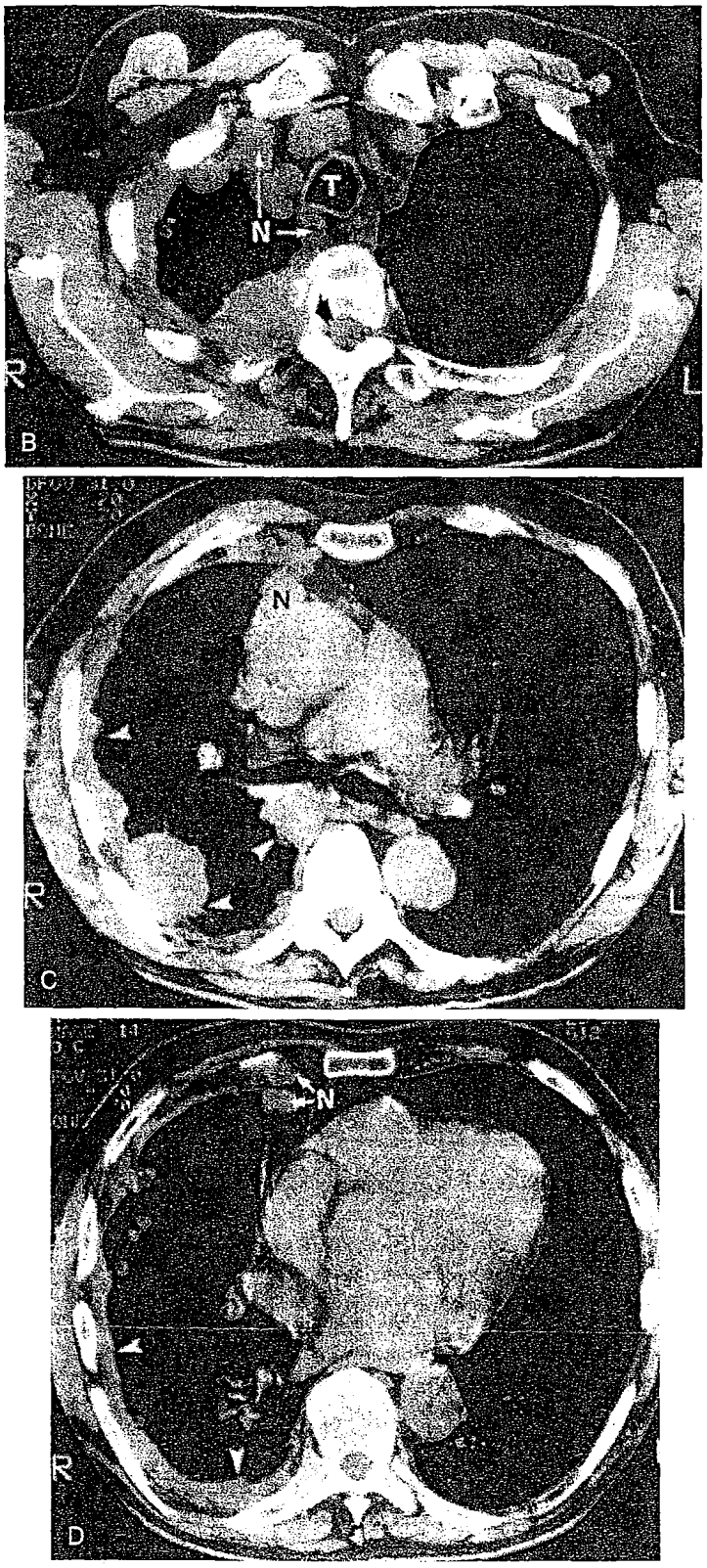


**Figure 60–46** *Continued.* CT scans through the upper *(B)*, middle *(C)*, and lower *(D)* thorax confirm the extensive right pleural thickening *(arrowheads)* and demonstrate extrapleural extension of the neoplasm in and around the ribs and vertebra *(closed arrows)* and within some of the mediastinal lymph nodes (N). The diagnosis of mesothelioma was confirmed at autopsy several months later.

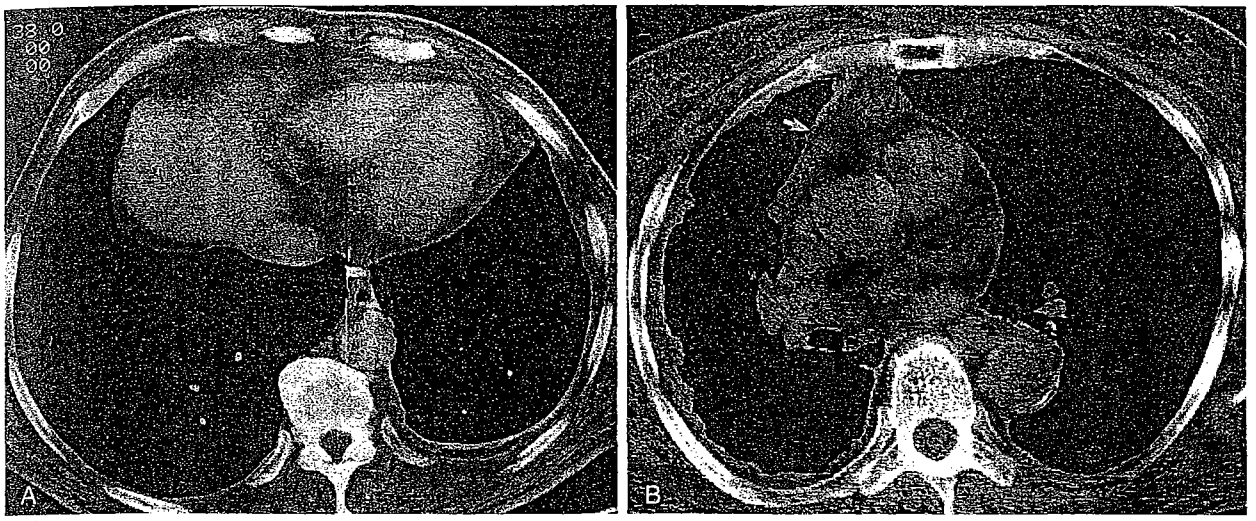


**Figure 60–47. Benign Versus Malignant Pleural Thickening.** A conventional 10-mm collimation CT scan *(A)* in a 59-year-old man demonstrates extensive thickening of the posteromedial, lateral, and anterior aspects of the left pleura; the mediastinal pleura is uninvolved. The patient had been exposed to asbestos many years before as a carpenter. Pleural biopsy specimens demonstrated only fibrosis. A CT scan in an 80-year-old woman *(B)* demonstrates extensive right pleural thickening. Involvement of the mediastinal pleura *(arrows)* as well as nodular appearance of the pleural thickening is evident. Biopsy demonstrated mesothelioma.

Significant enhancement may occur with intravenous contrast administration.[690, 691]

As indicated previously, the majority of cases follow asbestos exposure; however, some have been described in association with other causes of pleural thickening or effusion.[689, 692] The lesion may develop and progress over a few months or several years. In one series of 74 patients, it occurred on a background of benign asbestos pleurisy in 9 and slowly increasing pleural thickening in 13;[692] in the remaining 39 patients, it was a new finding, earlier radiographs showing only plaques or being normal. The magnetic resonance appearance has been described in one patient.[693] Similar to CT, it demonstrated the abnormality as a peripheral mass abutting an area of pleural thickening with associated vessels curving into the area of atelectasis. Curved low-signal lines within the atelectatic lung were postulated to be caused by indentations of the visceral pleura.[693] Round atelectasis is not metabolically active on 2-[$^{18}$F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET).[693a] FDG-PET imaging therefore can be helpful in differentiating the abnormality from pulmonary carcinoma.[693a]

### Clinical Manifestations

The great majority of patients who have pleuropulmonary asbestos-related disease have no symptoms.[449, 669] Benign pleural effusions may or may not be associated with pleural pain.[556, 694–696] They are recurrent in 15% to 30% of cases,[696, 697] are usually smaller than 500 ml, are often serosanguineous,[556, 696, 697] and persist from 2 weeks to 6 months.[696, 697] Although they can occur in the absence of pleural plaques, more often these are present at the time of effusion.[697] In one study of 22 patients who had benign pleural effusion attributed to asbestos exposure, the mean duration of exposure was 5.5 years (in one case, it was said to occur after only 2 weeks), and the mean interval between exposure and presentation was about 16 years.[696] Persistent pleuritic pain with intermittent pleural friction rubs has been described in some patients.[696]

In the absence of underlying chronic obstructive pulmonary disease, breathlessness is usually associated with pulmonary interstitial fibrosis; occasionally, it is caused partly or entirely by diffuse pleural fibrosis.[423, 508, 699–702] In patients who have asbestosis, shortness of breath seldom develops sooner than 20 to 30 years after initial exposure.[703, 704] It is usually progressive, despite discontinuation of asbestos exposure. Prolonged asbestos exposure can also cause cough, either dry or productive of mucopurulent sputum; this symptom can be present with or without dyspnea on exertion and in the absence of radiographic or physiologic evidence of asbestosis.[705] In one cohort study of asbestos workers, wheeze and dyspnea were associated with a significant risk for restrictive lung function impairment;[706] smaller but similar functional deficits were associated with a history of cough, sputum production, and chronic bronchitis.

Physical examination may reveal evidence of deformity of the thoracic cage caused by underlying pleural disease, even in asymptomatic patients. Pleural effusion may be suggested by unilateral or bilateral dullness on percussion and decreased breath sounds. Crackles are common at the lung bases in workers who have had prolonged exposure to asbestos;[707] in two studies, they were present in about one third of workers compared with only 5% of control subjects.[708, 709] They are particularly common in patients in whom the diagnosis of asbestosis has been made radiographically,[710] being found in 58% in one series[711] and in 64% in another.[712] In one study in which time-expanded waveform analysis was employed, fine crackles were detected in all 12 patients who had asbestosis;[713] differences in the timing and nature of the crackles could be discerned between patients who had left ventricular failure and those who had asbestos-related pleural disease. The presence of crackles also correlates with derangement of pulmonary function.[710]

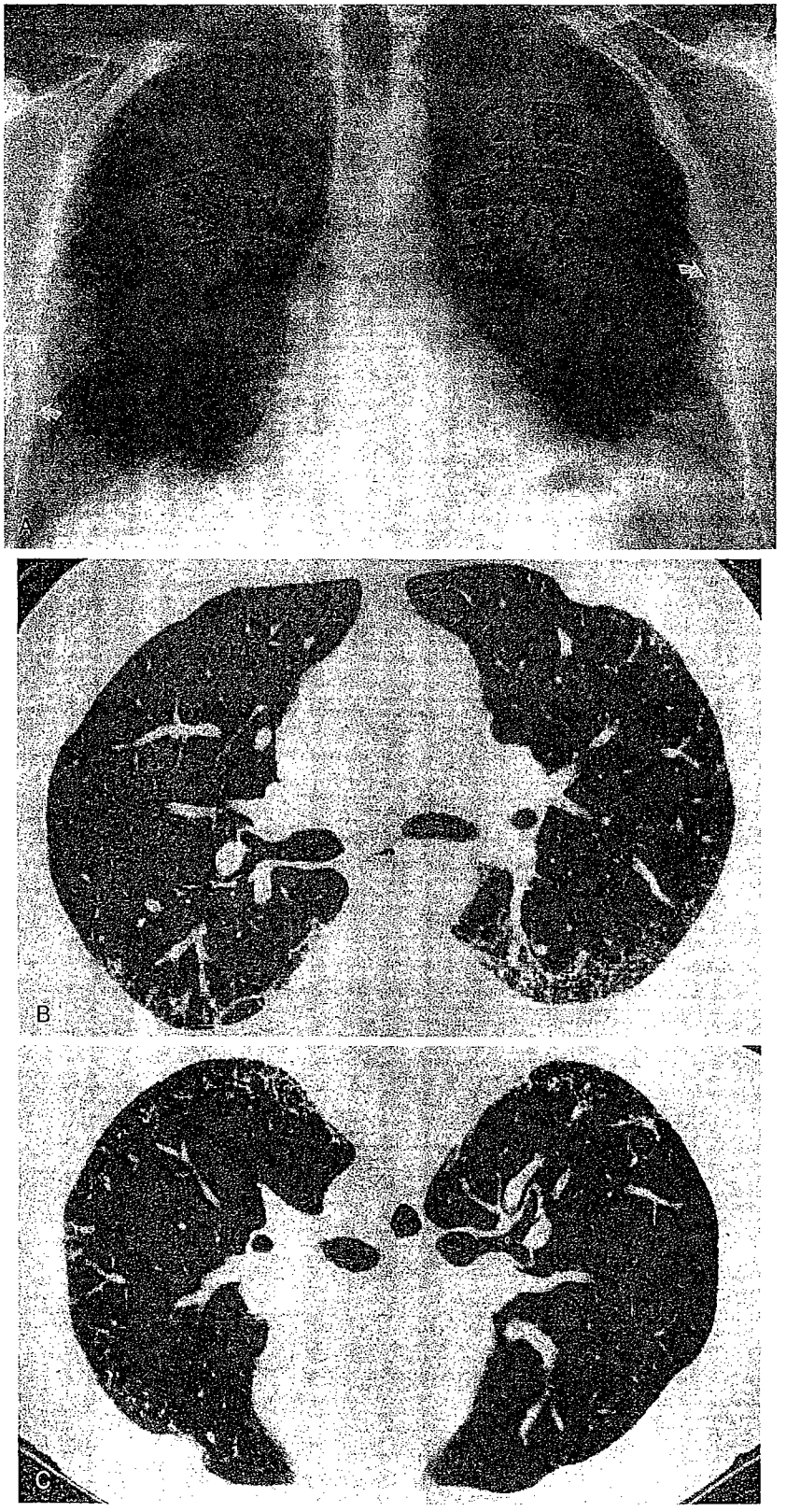


**Figure 60–48. Asbestosis.** A posteroanterior chest radiograph *(A)* in a 54-year-old shipyard worker demonstrates irregular linear opacities in the lower lung zones. Note associated low lung volumes and bilateral pleural plaques *(arrows)*. HRCT scans in the supine *(B)* and prone *(C)* positions demonstrate irregular linear opacities involving predominantly the subpleural lung regions. The opacities represent both intralobular lines and thickening of interlobular septa. Localized areas of ground-glass attenuation in the subpleural lung regions are also evident.

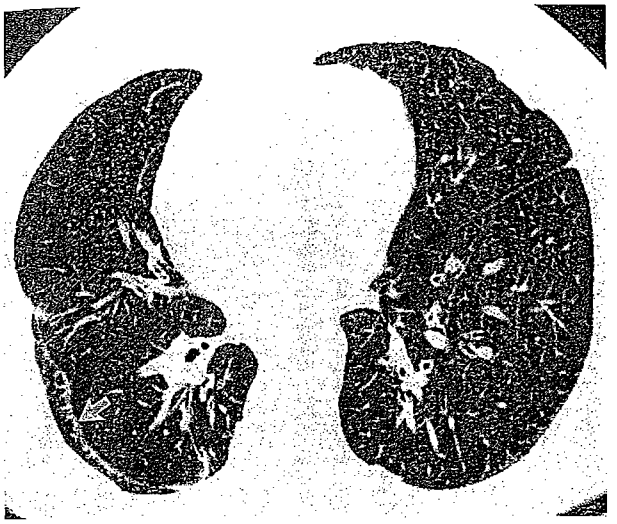

**Figure 60–49. Subpleural Curvilinear Opacities in Asbestosis.** An HRCT scan demonstrates a subpleural curvilinear opacity in the right lung running parallel to the pleura *(arrow)*. Bilateral pleural plaques and evidence of early fibrosis in the posterior aspect of the left lung are also present. The parenchymal abnormalities did not change in the prone position. The patient was a 58-year-old shipyard worker.

Finger clubbing is also a frequent sign in asbestosis,[704] having been observed in 32% of patients in one series[711] and in 42% in another.[712] The prognostic significance of the finding was evaluated in 167 patients who had asbestosis certified by the London Pneumoconiosis Medical Panel from 1958 to 1975.[714] In the individuals who had clubbing, it was found to develop early in the clinical course of the disease and to be associated with a lower diffusing capacity, a higher mortality rate, and a greater likelihood of progression of pulmonary fibrosis than in those who did not. Thus, its presence is an indication of a more severe form of disease; however, finger clubbing was not associated with heavier asbestos exposure. If the patient lives long enough and survives complicating mesothelioma or pulmonary carcinoma, signs of cor pulmonale may develop. Rarely, patients who have asbestosis develop chronic constrictive pericarditis.[715]

### Pulmonary Function Tests

Patients who have asbestosis usually show a restrictive pattern of pulmonary function, with decreased vital capacity, residual volume, and diffusion capacity and preservation of relatively good ventilatory function.[718, 719] Many patients, however, show some degree of airway obstruction as well as a result of asbestos-induced bronchiolar fibrosis and narrowing[720–722] or enhancement of the effects of cigarette smoking.[723] In addition, the prevalence of CT-diagnosed emphysema in workers who have early asbestosis (54%) has been found to be double that of those who do not;[233] such emphysema undoubtedly contributes to the air-flow obstruction. Because many asbestos workers smoke cigarettes, the measurement of total lung capacity (TLC) by itself is an insensitive means of assessing functional impairment in asbestosis.[724] Many workers who have significant asbestosis have normal or increased TLC as a result of the presence of associated air-flow obstruction.[724, 725] Therefore, helium dilution methods are particularly unsuitable for assessing lung volumes in these patients.[727] An accelerated decline in lung function has been noted in dust-exposed workers in the absence of a clinical and radiographic diagnosis of asbestosis.[721, 728, 729] Pulmonary compliance characteristically is greatly reduced[215, 704, 707, 730–732] and may be an early marker of pulmonary fibrosis when the chest radiograph is normal.[733]

Hypoxemia may be observed on exercise, but the $P_{CO_2}$ is usually normal or low. One group of investigators found a ratio of $P(A\text{-}a)O_2/\dot{V}O_2$ greater than 35 during exercise to be quite specific for asbestosis in a group of workers who had a spectrum of asbestos-related disorders, including air-

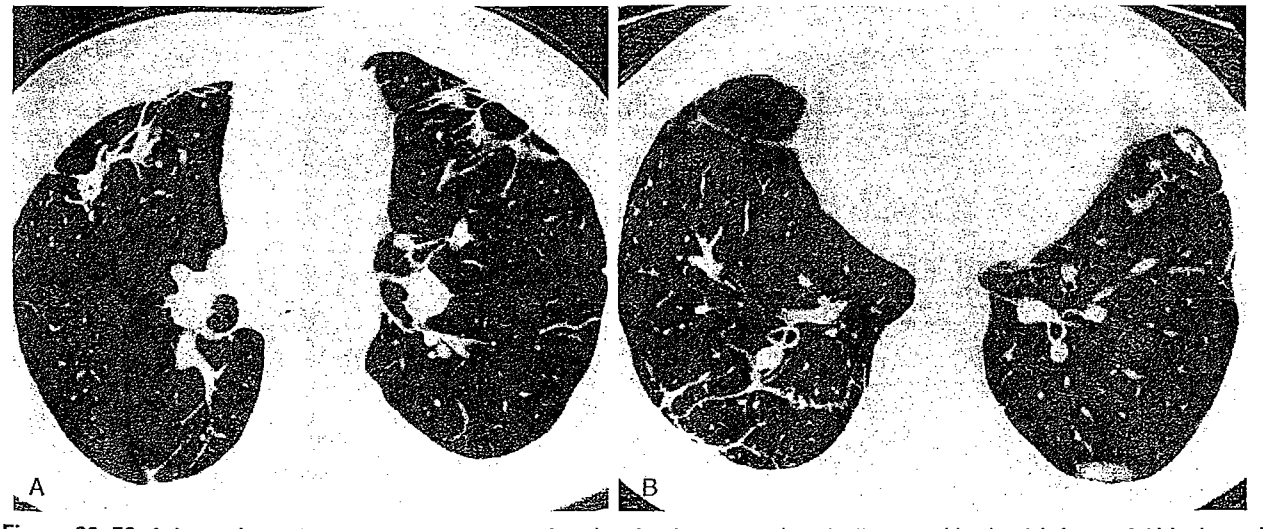


**Figure 60–50. Asbestosis.** An HRCT scan in a 45-year-old shipyard worker demonstrates irregular linear opacities, interlobular septal thickening, and evidence of architectural distortion in the anterior aspect of the midlung zones *(A)*. Irregular thickening of interlobular septa in the right lower lobe *(B)* is also evident.

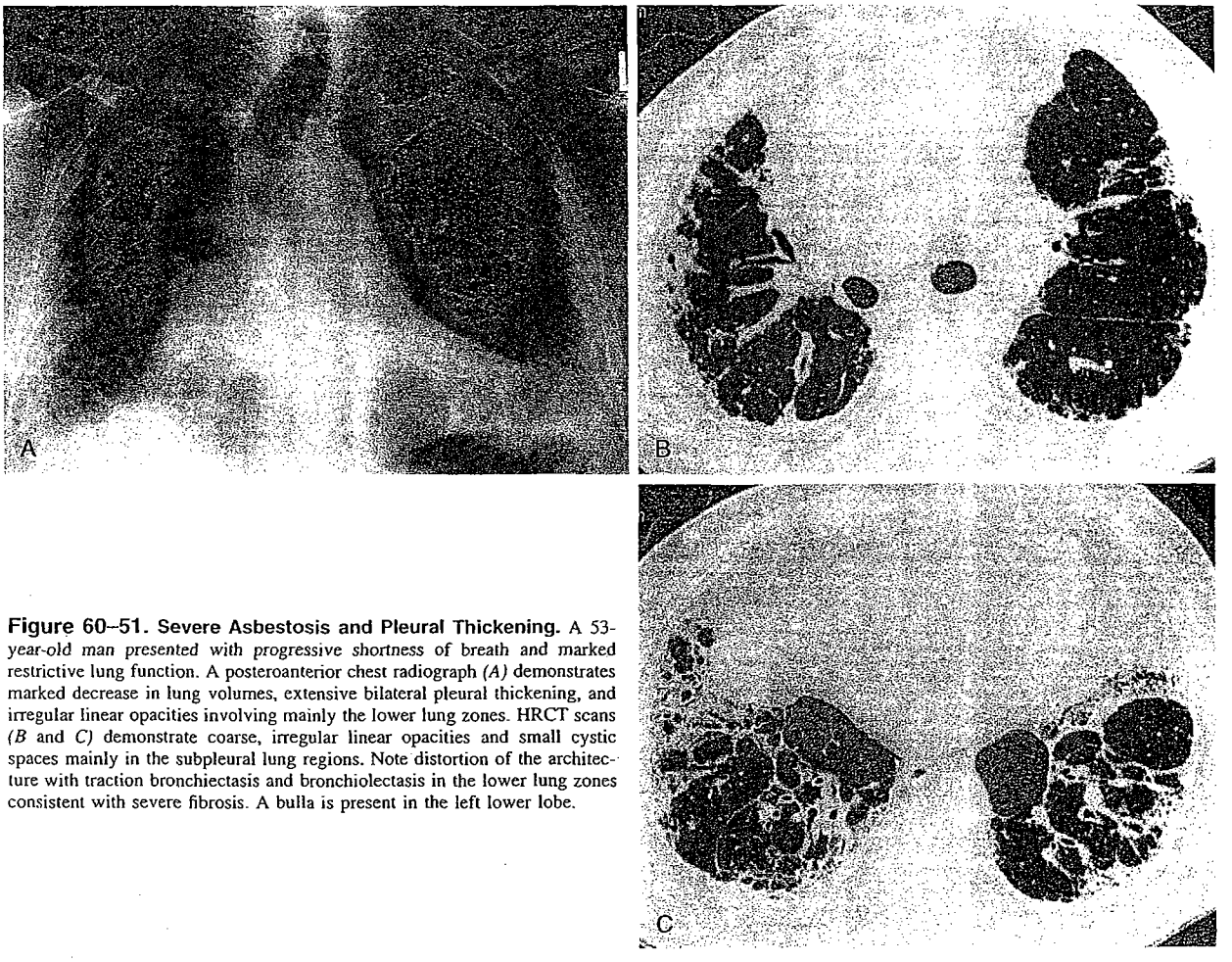


**Figure 60–51. Severe Asbestosis and Pleural Thickening.** A 53-year-old man presented with progressive shortness of breath and marked restrictive lung function. A posteroanterior chest radiograph *(A)* demonstrates marked decrease in lung volumes, extensive bilateral pleural thickening, and irregular linear opacities involving mainly the lower lung zones. HRCT scans *(B* and *C)* demonstrate coarse, irregular linear opacities and small cystic spaces mainly in the subpleural lung regions. Note distortion of the architecture with traction bronchiectasis and bronchiolectasis in the lower lung zones consistent with severe fibrosis. A bulla is present in the left lower lobe.

flow obstruction and pleural disease;[734] however, the measurement lacked sensitivity. Employing electron microscopic and stereologic techniques, another group concluded that measurable diffusion abnormalities were caused chiefly by ventilation-perfusion imbalance rather than increased thickness of the alveolar septa.[734a]

In one investigation in which the radiographic and functional characteristics of patients who had asbestosis were compared with those of patients who had idiopathic pulmonary fibrosis, pulmonary function was found to be better in patients who had asbestosis than in those who had idiopathic pulmonary fibrosis with the same degree of radiographic parenchymal abnormality.[735] Patients who have idiopathic pulmonary fibrosis also have worse gas exchange on exercise than do those who have asbestosis,[736] the former having greater falls in arterial oxygen saturation and higher levels of dead space ventilation.

It has become clear that asbestos-related pleural disease can also affect lung function adversely.[718, 721, 737, 738] Both pleural plaques and diffuse pleural thickening cause decreases in vital capacity, although the effects of diffuse thickening are more marked.[719, 739–741] Some investigators have linked the presence of asbestos pleural disease to the finding of air-flow obstruction greater than that expected for the degree of cigarette smoking;[742–744] this finding might be explained by concomitant asbestos-related airway disease. When restriction is the result of diffuse pleural thickening, correction of the diffusing capacity for alveolar volume gives a higher coefficient of diffusion that may not accurately reflect the severity of any accompanying parenchymal fibrosis.[745, 746]

Exercise testing is often used to evaluate asbestos-exposed workers as part of compensation assessment. In one group of 120 asbestos-exposed workers who were seeking compensation, a large number were limited by cardiac function.[747] This finding contrasts with those of later studies, in which patients who had diffuse pleural thickening alone or pleural plaques had ventilatory abnormalities on exercise, with normal cardiovascular responses;[748, 749] in these patients, there was excessive ventilation, high dead space ventilation, and (sometimes) oxygen desaturation, the last-named suggesting the presence of underlying occult pulmonary fibrosis.

### Diagnosis

In the presence of characteristic radiographic findings, the diagnosis of asbestos-related disease should be based

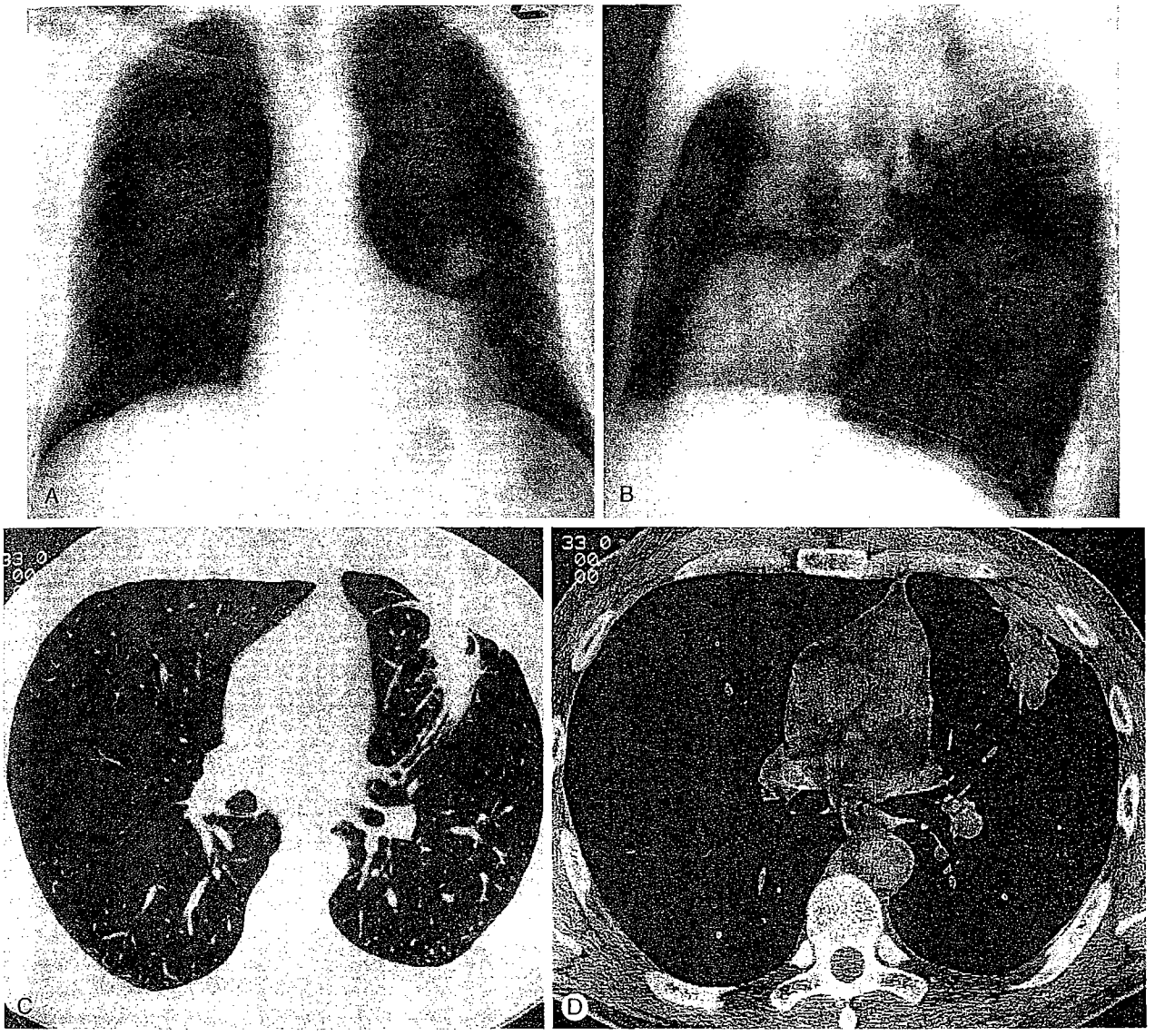


**Figure 60–52. Round Atelectasis.** A 54-year-old man with a long-standing history of exposure to asbestos was referred for evaluation of a suspected left lung mass. Posteroanterior *(A)* and lateral *(B)* chest radiographs demonstrate evidence of left pleural thickening and a 3-cm mass in the left lung. The margins of the mass are poorly defined, indicating that it is pleural based. An HRCT scan *(C)* demonstrates an oval soft tissue mass in the lingula associated with loss of volume and anterior displacement of the major fissure. Vessels and bronchi can be seen curving into and sweeping around the area of atelectasis. Soft tissue windows *(D)* demonstrate that the area of atelectasis abuts a focal area of pleural thickening. The size of the mass was stable over a 3-year follow-up period.

primarily on a complete occupational history;[750] if this is not forthcoming, inquiry should be directed toward the possibility of nonoccupational exposure. This approach applies to women as well as to men, not only because of the potential for significant asbestos exposure from the cleaning of clothes of occupationally exposed male members of the family, but also because women may have been occupationally exposed as well, sometimes remotely.[454, 751, 752] The combination of a history of exposure, positive radiographic findings, bibasilar fine crackles, clubbing, and impaired pulmonary function (including significant reductions in vital capacity, diffusing capacity, and compliance) is virtually diagnostic of asbestosis.[426]

As indicated previously, BAL can be useful in establishing asbestos exposure,[753–755] although the absence of asbestos bodies by this technique does not exclude the diagnosis of asbestos-associated disease.[756] The yield of asbestos bodies at bronchoscopy can be increased by performing lavage in the lower lobes.[757] In comparison with BAL, sputum examination is an insensitive method of assessing lung asbestos burden; however, when asbestos bodies are identified in these specimens, a high lung asbestos burden is likely.[758] Lung biopsy can confirm a suspected diagnosis but is seldom indicated; in fact, in the presence of advanced disease, it can be a hazardous procedure.[759] Electron microscopic examination of transbronchial biopsy specimens has been reported

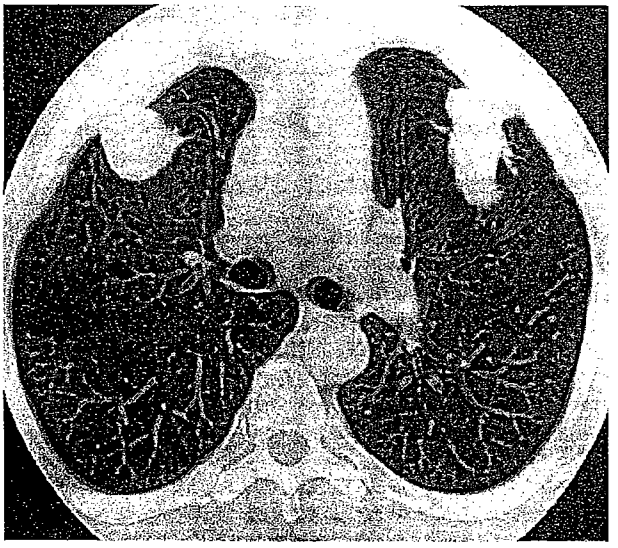

**Figure 60–53. Bilateral Round Atelectasis.** A 10-mm collimation CT scan in a 58-year-old patient demonstrates bilateral round atelectasis. Vessels and bronchi can be seen sweeping around and into the focal area of atelectasis. There is evidence of volume loss with anterior displacement of the right upper lobe bronchi. The bilateral areas of atelectasis abut calcified pleural plaques. (Courtesy of Dr. Louise Samson, Hotel Dieu de Montréal, Quebec.)

to be useful in establishing low-level occupational exposure.[760] The procedure also may be useful in determining unsuspected asbestos exposure in open-lung biopsy specimens, thus avoiding an inappropriate diagnosis of idiopathic pulmonary fibrosis.[761]

The chest radiograph is normal in 10% to 20% of patients in whom there is histologic evidence of fibrosis.[762] This situation raises the question as to what the minimal diagnostic criteria for asbestosis should be and how the diagnosis can be made in workers who have normal chest radiographs. As discussed previously, HRCT is clearly a more sensitive tool for the appreciation of early pulmonary fibrosis than radiography.[763–769] In workers who have an appropriate exposure history, latency from first exposure to dust, and pulmonary function disturbance, the diagnosis of asbestosis can be confirmed by HRCT, even if the radiograph is normal. Many patients who have a normal or equivocal chest radiograph and a history of significant asbestos exposure have an abnormal gallium scan;[770] the majority of these go on to develop radiologic evidence of asbestosis.[409] HRCT, however, has largely supplanted this test in the investigation of patients who have equivocal evidence of asbestosis after other investigations.

A poorly defined opacity in the periphery of a lung of a patient who has asbestos-related pleural disease often represents round atelectasis; although the radiologic appearance is characteristic, particularly on CT, transthoracic needle aspiration may be required to rule out carcinoma.[612, 613, 771, 772]

### Prognosis and Natural History

The two most important complications of asbestos inhalation are pulmonary fibrosis and pleuropulmonary malignancy. The likelihood of developing clinically evident asbestosis depends (at least in part) on cumulative dust exposure and time from first contact with the mineral. Disabling respiratory disease and cor pulmonale usually develop only in those individuals who have a history of heavy dust exposure and then typically 30 or more years after initial contact. The mortality related to asbestosis increased in the United States between 1970 and 1990, from 0.49 per million persons to 3.06 per million.[773] Because dust control measures have been in place in the United States and most other "developed" countries since the 1960s, the number of patients who have such severe disease can be expected to peak in the 1990s and to fall thereafter. The 10-year risk of death as a result of asbestosis increases significantly with increasing severity of baseline fibrosis, as assessed clinically, functionally, and radiographically.[773]

Of all nonneoplastic pulmonary diseases, those related to asbestos have the highest incidence of associated neoplasia, especially pulmonary carcinoma and pleural mesothelioma.[774, 775] In a cohort study of 11,000 Quebec chrysotile workers, the standardized mortality rates for pulmonary carcinoma and mesothelioma were 1.4 and 25, respectively;[776, 777] of the 5,350 individuals who died between 1975 and 1992, approximately 320 died of pulmonary carcinoma, 48 of asbestosis, and 25 of mesothelioma. There has been vigorous debate in the literature about when the cancer risk of asbestos was first recognized;[778] however, since the mid-1950s, the relationship has been documented in numerous pathologic and epidemiologic studies.[774, 779, 780] A latent period of at least 20 years from the time of first exposure to the development of malignancy is characteristic.[781] The degree of exposure, as indicated by occupational history and the number of asbestos bodies or fibers in lung tissue, is usually high.[431, 782–787] Most,[750, 788, 789] albeit not all,[782] investigators have found that the relationship between malignancy and asbestos exposure is linear. These issues are discussed in greater detail on pages 1074 and 2807.

A variety of extrathoracic neoplasms have also been reported to have an increased frequency after asbestos exposure, the one with the closest association probably being peritoneal mesothelioma.[790, 791] A number of workers have also found evidence for an increased incidence of gastrointestinal,[447, 792, 793] renal,[794] oropharyngeal,[794] and laryngeal[795–798] carcinoma as well as leukemia[793, 799] and lymphoma.[800] In addition to malignancy, excess mortality of asbestos-exposed workers is seen from nonmalignant respiratory disease.[801] In one intriguing study, a relative risk of death from ischemic heart disease of 3.5 was reported in a group of workers who had asbestosis compared with a similarly exposed group without lung function abnormalities.[802] Other investigators have not shown an excess risk of deaths from ischemic heart disease in asbestos-exposed populations,[802] even in workers most heavily exposed to dust;[803] however, this failure could be related to the "healthy worker" effect.

In contrast to patients who have silicosis, those who have asbestosis do not appear to be at greater risk for tuberculosis than the general population;[804] however, in one large study of causes of death among miners and millers of crocidolite in Western Australia, an excess mortality from the infection was found.[805]

## OTHER SILICATES

As discussed previously, it is important to make a distinction between silica (i.e., $SiO_2$) and silicates (which consist of $SiO_2$ combined with one or more cations). Silica is clearly a highly toxic substance that is the cause of many cases of pulmonary disease. Although silicates are also generally toxic to cells in tissue culture, with the exception of asbestos this capacity appears to be poorly expressed *in vivo*, and pulmonary disease is uncommon or rare after their inhalation. In fact, the pathogenicity of some of the minerals is open to question even when disease is present because other substances that are clearly toxic, such as asbestos or silica itself, are commonly inhaled at the same time as the silicate.

Because silicates are crystalline, they can be identified as birefringent, needle-shaped or platelike particles on polarization light microscopy. Although the size and shape of such particles may suggest their nature, definitive identification of the specific mineral usually requires the use of energy-dispersive x-ray spectroscopy or analysis of tissue digests.

### Talc

Talc is a hydrated magnesium silicate that usually occurs in the form of sheetlike crystals that are easily cleaved into thin plates.[807] It is used in the manufacture of such diverse products as leather, rubber, paper, textiles, ceramic tiles, and roofing material. It is also used as an additive in paint, food, many pharmaceuticals, cosmetics, insecticides, and herbicides. Individuals in any of these occupational settings may be exposed to potentially harmful levels of dust. Others at risk include workers involved in talc mining and milling,[808–810] individuals who work with soapstone,[811, 812] and workers exposed to commercial talcum powder.[813–815] Pulmonary disease related to talc can also develop in nonoccupational settings by several mechanisms, including (1) accidental inhalation of talcum powder in small children, a process that may be associated with acute fatal respiratory insufficiency as a result of tracheobronchial obstruction;[816, 817] (2) intravenous injection of oral medications containing talc as a filler, a form of microembolization discussed in detail in Chapter 49 (*see* page 1857); (3) obsessional inhalation of commercial talcum powder;[813] and (4) rarely, following talc pleurodesis, as in one patient who developed bilateral interstitial disease and pleural effusion.[818] (Despite the common contamination of talc with asbestos, there appears to be little, if any, risk for the development of mesothelioma after talc pleurodesis.[819])

Because other elements, such as iron and nickel, are usually incorporated within the talc crystal and because the substance is often found in association with other minerals, such as quartz, mica, kaolin, and various types of asbestos, the composition of commercially available talc is quite variable from region to region and from industry to industry.[807, 810, 820, 821] As a result, the pattern of pulmonary disease associated with its inhalation is variable, leading to the use of such terms as *talco-asbestosis*, *talco-silicosis*, and *pure talcosis*.[822] Although there is no doubt that talc itself can induce a foreign body giant cell reaction, its ability in pure form to induce fibrosis has been put into question by the results of both epidemiologic and animal studies;[807] in fact, it has even been suggested that the majority, if not all, of the functionally and radiologically significant pulmonary abnormalities associated with talc are caused by other substances. It seems likely, however, that true inhalational talcosis does occur, as evidenced by reported cases in which significant pulmonary disease has been caused by exposure to dust apparently uncontaminated by asbestos or silica.[812, 822–824] As might be expected, there appears to be an association between the degree of exposure and the risk of development of pleuropulmonary disease.[810]

Pathologic findings are variable and, as indicated, may be caused in some cases by asbestos or silica rather than talc alone.[812, 822] Abnormalities include pleural fibrosis (sometimes with calcification and plaque formation identical to that seen in asbestos-related pleural disease), foci of nodular or stellate parenchymal fibrosis, more or less diffuse interstitial fibrosis (Fig. 60–54), and peribronchiolar and perivascular macrophage infiltrates.[823] Nonnecrotizing granulomatous inflammation has been identified in some cases.[823, 825] Macrophages and multinucleated giant cells containing irregularly shaped birefringent plates or needle-like crystals, representing ingested talc, are common (*see* Fig. 60–54). Talc-associated ferruginous bodies are also frequent.[823] Occasionally, talc is minimal or absent on routine histologic examination, its presence being identified only with the use of scanning electron microscopy.[825] In suspected cases, optical and electron microscopy may reveal talc particles in BAL fluid.[818, 820]

The principal radiologic abnormality is pleural plaques similar to those of asbestos-related disease. They may be massive and extend over much of the surface of both lungs.[809, 810, 826, 827] Occasionally, they involve the pericardium. In one study of 221 workers exposed to tremolite talc, pleural plaques were seen in 14 (6%).[646] Parenchymal involvement is said to be similar to that in asbestosis,[827–829] the radiographic pattern being one of general haziness, nodulation, and reticulation, with sparing of the apices and costophrenic sulci.[809, 829] Some cases may show confluence of lesions, creating large opacities (Fig. 60–55).[830]

When present, symptoms are similar to those of other pneumoconioses and include dyspnea and productive cough. Decreased breath sounds (presumably related to pleural thickening), crackles at the lung bases, limited chest expansion, and finger clubbing may be found on physical examination.[827, 831] As with other minerals, disease may become menifest many years after exposure has ceased, and careful occupational history taking may be necessary to reveal its presence.[806] Serum angiotensin-converting enzyme is increased in some patients.[832]

Compared with other minerals, such as asbestos and silica, talc appears to be a relatively innocuous substance. For example, in one study of 110 men employed in the mining and processing of soapstone in Sweden, only 5 individuals (all who had at least 20 years' exposure) showed radiographic evidence of pneumoconiosis;[811] in all 5, this was minimal and was unassociated with clinical impairment. Epidemiologic studies of individuals exposed to talc have shown increased mortality from nonmalignant respiratory disease and an increased risk of pulmonary carcinoma.[833, 834] With respect to malignancy, it is likely that other agents, such as radon and asbestos, are more important than talc

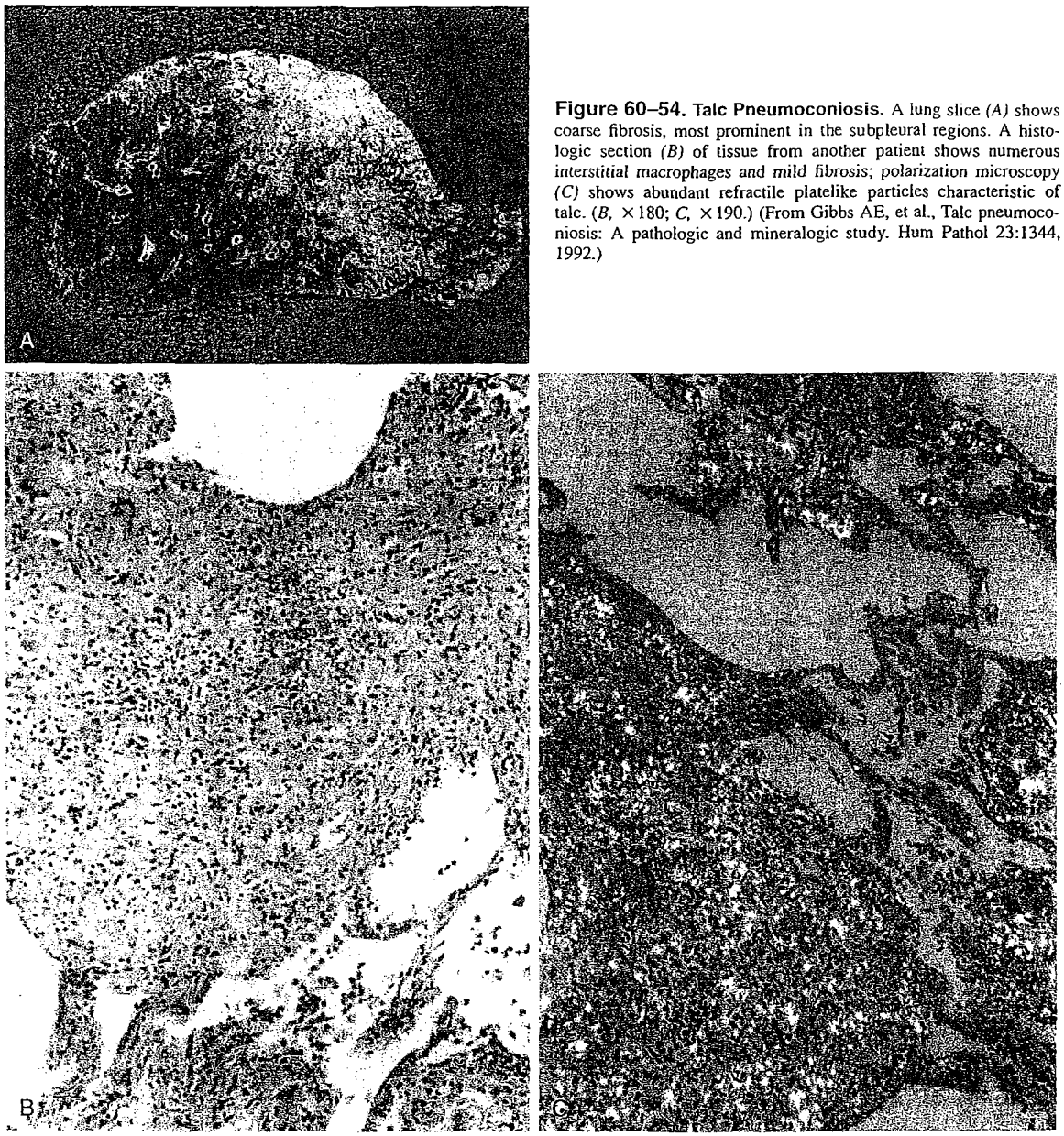


**Figure 60–54. Talc Pneumoconiosis.** A lung slice *(A)* shows coarse fibrosis, most prominent in the subpleural regions. A histologic section *(B)* of tissue from another patient shows numerous interstitial macrophages and mild fibrosis; polarization microscopy *(C)* shows abundant refractile platelike particles characteristic of talc. (*B*, ×180; *C*, ×190.) (From Gibbs AE, et al., Talc pneumoconiosis: A pathologic and mineralogic study. Hum Pathol 23:1344, 1992.)

itself.[833–835] A possible association with nontuberculous mycobacterial infection has been hypothesized.[835a]

Decreases in vital capacity, TLC, and DLCO have been reported in many exposed workers.[836, 837] DLCO is said to correlate with the extent of parenchymal involvement seen radiographically. Restrictive pulmonary function impairment has been described in patients who have pleural disease only.[810, 838]

### Mica

Micas are complex aluminum silicates, of which three forms are commercially available:

1. *Muscovite*, a potassium compound that, because of its transparency and resistance to heat and electricity, is used in the manufacture of windows for stoves and furnaces; the substance is also an important constituent of slate (along with quartz), and workers involved in the mining and use of this substance (e.g., in roofing, highway construction, and tiling) have been reported to develop a distinctive pneumoconiosis.[839]

2. *Phlogopite*, a magnesium compound that is used in the electrical industry.

3. *Vermiculite*, another magnesium compound whose uses relate primarily to its fire resistance and its insulation and ion-exchange properties; it is also used as a filler in many substances (such as soil, animal feed, adhesives, cements, and enamels) and a carrier for various chemicals, including herbicides, insecticides, fungicides, and fertilizers.[840]

Similar to talc, micas are often associated with other minerals, particularly tremolite asbestos,[840] and the possibility that

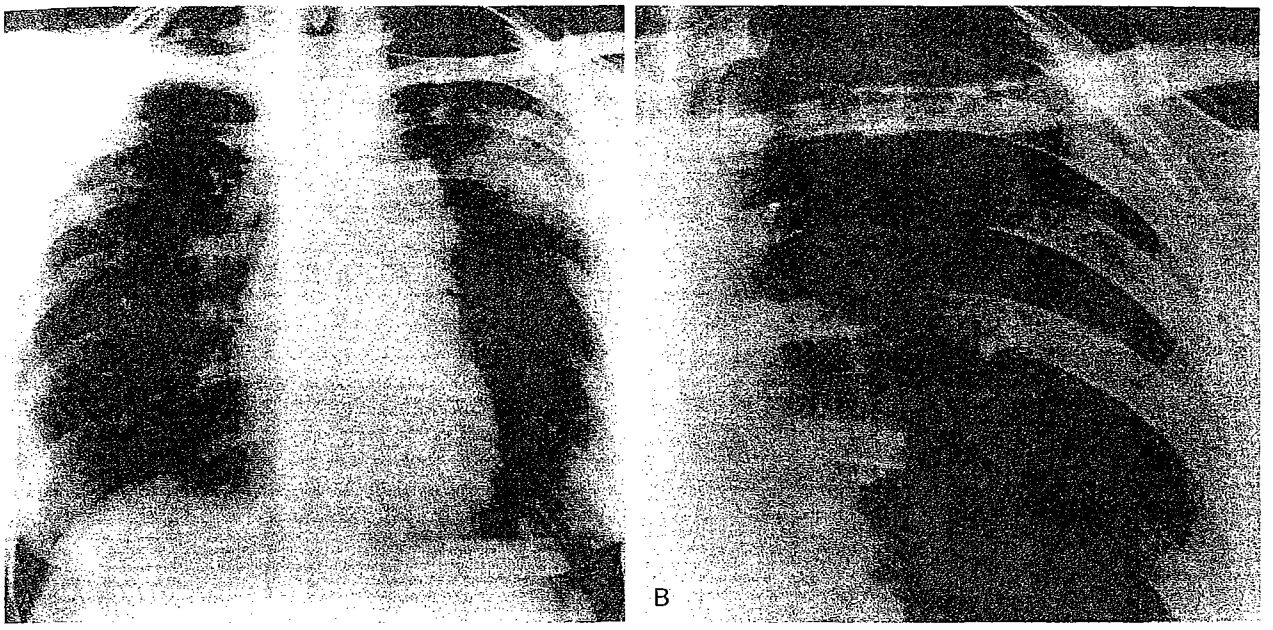


**Figure 60–55. Pulmonary Talcosis.** A 31-year-old woman had noted the onset of dyspnea on exertion several months previously and at the time of this radiograph could climb only 10 stairs without stopping. She had to use two pillows to sleep, and on occasion she awoke during the night gasping for breath. There was no cough or recent hemoptysis. A posteroanterior radiograph *(A)* reveals extensive involvement of both lungs by a rather coarse reticular pattern. In the upper axillary zone on the right and in the left midlung *(B)* are two areas of homogeneous consolidation possessing poorly defined margins. Paratracheal lymph node enlargement is present bilaterally, more marked on the left. At thoracotomy, biopsy specimens obtained from lung and lymph node revealed multiple foci of dense fibrosis lying in close proximity to blood vessels and containing extremely numerous, doubly refractile crystals. In view of these findings, the patient was questioned further and finally admitted to an extraordinary history of excessive inhalation of lavender-scented talcum powder during a 3-month period when she was pregnant 2 years previously. She was in the habit of spreading the talcum powder liberally over the pillow and blankets at night and actually inhaled it in large amounts from her cupped hands. Subsequent assay of the particles observed histologically proved them to be talc.

they can cause disease by themselves has been questioned.[841] For example, workers exposed to vermiculite contaminated with fibrous tremolite have been found to have a high incidence of benign pleural effusion, plaques, and pleural thickening,[840] abnormalities well known to be caused by asbestos alone. In addition, although there have been many reports of possible pneumoconiosis caused by micas,[840, 842–844] the documentation of the relationship between occupational exposure and pathologic findings has not always excluded other causative agents. Thus, although a literature review in 1985 documented 66 cases reported as mica pneumoconiosis, the evidence that it was caused by mica exposure alone was considered by the authors to be reasonably convincing in only 26.[845] Animal experiments have demonstrated the substance to have little or no fibrogenic activity,[846] although the validity of these studies has, in turn, been questioned.[845] Despite these uncertainties, occasional cases have been reported in which apparently pure mica exposure has been associated with pulmonary fibrosis,[841, 847] and it seems reasonable to conclude that the risk of developing pulmonary disease from mica inhalation is present but slight. Radiographic and clinical manifestations are indistinguishable from those associated with exposure to asbestos or talc.[646]

### Fuller's Earth

The term *Fuller's earth* refers to a variety of clays with different chemical compositions that were formerly used in the process of fulling (removing grease from wool) and are now employed in the refining of oils, in filtering and purification, in the bonding of molding sands in foundry work, and as a filler in cosmetics and pharmaceuticals. Prolonged exposure to the substance in these occupations or during its mining or milling has been associated with simple pneumoconiosis and, occasionally, PMF.[835, 848] Although it is likely that some of these cases are the result of concomitant silica exposure,[848] the possibility of a toxic action of the clays has not been excluded.

Pathologic changes associated with exposure to Fuller's earth occur mainly in the upper lobes and consist of an increase in reticulin surrounding dust particles, with little fibrosis or cellular reaction.[849, 850] Radiographic changes are said to consist of a prominence of bronchovascular markings and, in some cases, PMF.[851]

### Kaolin

The term *kaolin* (china clay, ball clay, fire clay) derives from the Chinese *Kauling* or high ridge, the name given a hill near Jauchau Fu, China, where the clay was first mined.[852] It actually designates a group of clays, of which kaolinite, a hydrated aluminum silicate, is the most important member. This substance is used industrially as a filler in plastics, rubber, paints, textiles, pharmaceuticals, and adhesives; as a coating for paper; as an absorbent;[853] and in the manufacture of firebricks.[854] Although water is usually

employed in quarrying or strip mining to minimize the risk of dust exposure, subsequent drying, bagging, and transporting can result in high concentrations of aerosolized kaolin and the potential for pulmonary disease. For example, in a study of 65 workers in a Georgia kaolin mine, pneumoconiosis occurred only in workers exposed in the processing area, where the mean respirable dust level was greater than 12 times that in the mine itself.[855] Exposure to kaolinite can also occur in workers involved in the mining, crushing, or grinding of china stone,[856] in which quartz is likely to be an important contaminant, and in the mining of shale.[11] Pulmonary disease has also been reported after the use of a liquid kaolin suspension for pleural poudrage in the treatment of recurrent spontaneous pneumothorax.[857]

Although it seems likely that kaolinite alone can cause pulmonary disease,[853, 858] it is probable that some cases are complicated by the inhalation of other particulates,[856] partly because the purity of raw clay varies considerably. For example, in some regions, such as Georgia in the United States, kaolin is relatively silica-free,[853] whereas in others, there is a substantial amount of admixed quartz and other minerals.

The incidence of chest disease varies in reported series. In one investigation, it was concluded that the general state of health in kaolin workers differed little from that of the regional general population of corresponding age and race.[859] By contrast, in a study of 553 Cornish china clay workers exposed to kaolin dust for periods exceeding 5 years, 48 (9%) showed clinical and radiographic evidence of pulmonary disease;[861] abnormalities were present in almost 25% of those exposed for more than 15 years. In another study of china clay workers from the same area, approximately three quarters were judged to have radiographs of category 0, 20% of category 1, and 5% of categories 2 and 3;[861] 19 workers (1%) were considered to have PMF. The prevalence of pneumoconiosis in Georgia kaolin workers has been estimated to be about 10%.[862] Although disabling pneumoconiosis is generally believed to develop in only a small proportion of affected individuals,[863–865] in one investigation of workers who processed kaolin in a Georgia mine, a significant degree of restrictive pulmonary dysfunction was found that correlated with the number of years of exposure.[866]

Pathologic features have been described in workers from Georgia[853] and Cornwall.[856] In the former, the features were similar to those of CWP, consisting of peribronchiolar macules containing numerous pigment-laden macrophages and interspersed reticulin fibers and of larger masses without definite anatomic localization that measured up to 12 cm in diameter. The latter were composed almost entirely of macrophages and only small amounts of collagen; coagulation necrosis and obliterative vascular changes similar to those seen in complicated CWP were also present. In the Cornish workers, variable degrees of interstitial and nodular fibrosis were seen, the latter correlating with the pulmonary quartz content.

The radiographic pattern varies. In some cases, there may be no more than a general increase in lung markings. With prolonged and severe exposure, a diffuse nodular and miliary mottling is present; when it develops, the appearance of PMF is identical to that seen in silicosis and CWP.[867, 868] Clinical findings are nonspecific. Complicating tuberculosis has been reported,[869] possibly in patients who have associated silicosis.

### Zeolites (Erionite)

Zeolites are a group of more than 30 naturally occurring minerals composed of hydrated aluminum silicates that are found in deposits of volcanic ash.[870] They are widely used as absorbents and for filtration. Most do not have a fibrous form and are not considered toxic; erionite, however, is fibrous and has been associated with a variety of pulmonary abnormalities. The richest deposits of this material are in Turkey and the western United States, particularly Nevada and Utah. The initial indication that the substance might be harmful came from Turkey, where epidemiologic studies revealed a high prevalence of pleural plaques, mesothelioma, and pulmonary carcinoma, apparently unassociated with asbestos exposure.[871–874] Subsequent investigators have also documented the presence of interstitial fibrosis.[870, 871, 874]

### Miscellaneous Silicates

An association between *mullite* (an artificial aluminum silicate used in the preparation of cat litter) and the presence of pulmonary disease has been documented in one report.[875] Affected patients complained of dyspnea and cough; some showed radiographic abnormalities consistent with fibrosis.

*Nepheline* is a mineral composed of sodium, potassium, and aluminum silicates that occurs in crystalline form in many igneous rocks; $SiO_2$ is bound to it in a complex crystal lattice. The rock is milled to a fine powder, which is used in the production of pottery glazes. At least three cases have been reported in which pneumoconiosis occurred as a result of exposure to the dust.[876, 877] The radiographic changes consist of diffuse interstitial disease, bilateral lymph node enlargement, and focal areas of atelectasis (presumably the result of airway compression by enlarged nodes).[877]

*Wollastonite* is a naturally occurring acicular or fibrous metasilicate used in ceramics and as a substitute for asbestos in some applications; it is similar in form, length, and diameter to the amphiboles.[878] There is fairly convincing radiographic and functional evidence that this substance can cause interstitial fibrosis,[878–880] although we are unaware of any pathologic studies confirming it.

*Taconite* is a low-grade ore consisting of iron, quartz, and numerous silicates, including cummingtonite-grunerite, a relative of amosite asbestos. Although there is some evidence that the substance may be fibrinogenic or carcinogenic, definite proof is lacking.[881, 882]

## INERT RADIOPAQUE DUSTS

### Iron

Workers in many occupations are exposed to dust containing a high content of iron, usually in the form of iron oxide ($Fe_2O_3$). When this substance is inhaled in sufficient quantity, it causes *siderosis*, a condition generally believed to be unassociated with fibrosis or functional impairment.

When the iron is admixed with a substantial quantity of silica, however, the resulting *silicosiderosis* (mixed-dust pneumoconiosis) can lead to appreciable pulmonary fibrosis and disability. This abnormality is potentially of some importance; for example, it was estimated in the early 1980s that approximately 4 million workers in the United States had had possible exposure.

The majority of affected individuals are electric arc or oxyacetylene torch workers, who are exposed to $Fe_2O_3$ in fumes derived from melted iron emitted during the welding process. Other cases of siderosis or silicosiderosis are found in individuals involved in the mining and processing of iron ores (such as hematite, magnetite, siderite,[884] and metallic pigments such as ochre), in workers in iron and steel rolling mills, in foundry workers (particularly those involved with cleaning steel castings[16, 17] and boiler scalers), and in silver polishers (*see* farther on).

As indicated previously, $Fe_2O_3$ inhaled in relatively pure form is believed to cause no significant inflammatory reaction or pulmonary fibrosis.[885] This belief is supported by the results of experimental studies in animals in which various iron compounds inhaled or injected intratracheally have not caused fibrosis.[886, 887] In addition, workers exposed for many years to $Fe_2O_3$ in high concentration are usually not disabled and show little evidence of fibrosis at autopsy, even when the iron content of their lungs is high.[17, 885, 888, 889]

Despite the relative benignity of pure siderosis, occupations associated with iron dust or fume production frequently generate other noxious materials. In fact, the mineral content of fumes derived from the welding process may be quite variable, depending on the composition of the metal being welded or of the welding electrode itself, or both. Among the additional materials that may be present are carbon, manganese, titanium, aluminum, various silicates (including asbestos), and free silica.[890] As the proportion of these substances in the fumes or dusts increases, the propensity for pulmonary damage and fibrosis also increases, resulting in the clinical, radiographic, and pathologic features characteristic of silicosiderosis. Although free silica is probably the most important agent responsible for the development of pulmonary disease in these circumstances, analyses of tissue and BAL fluid specimens have suggested that the fibrogenic reaction in some cases of welder's pneumoconiosis is also related to other substances.[891–893] Workers can also develop pulmonary disease as a result of a direct effect of toxic gases or fumes created during welding, resulting in several clinicopathologic syndromes (e.g., metal fume fever, chemical pneumonitis, hypersensitivity pneumonitis, and chronic bronchitis [*see* page 2174]).[890]

Pathologically, pure siderosis is characterized by the presence of $Fe_2O_3$ predominantly in macrophages in the peribronchovascular interstitium.[18, 895, 896] Iron-containing macrophages can also be seen within alveolar air spaces, particularly in individuals who were active welders at the time of death or biopsy (Fig. 60–56); these macrophages can frequently be detected in sputum specimens.[897] The iron may appear as an amorphous, tan-colored particle or may have a central black core. Although $Fe_2O_3$ does not react with Prussian blue, with time, many aggregates become associated with endogenous iron and thus stain with this dye. Fibrosis is usually absent or minimal in cases of pure $Fe_2O_3$ inhalation but is present to a variable degree if fibrogenic substances are also present;[896] in this situation, the appearance is similar to that of silicosis and is characterized by solitary or conglomerate nodules, the latter occasionally being large enough to be designated PMF (Fig. 60–57). In contrast to pure silicosis, however, the nodules are usually rather poorly defined and stellate. Aggregates of $Fe_2O_3$, either free or within macrophages, can often be found admixed within the fibrous tissue.

The radiographic pattern in pure siderosis is reticulonodular and widely disseminated (Fig. 60–58). In one evalua-

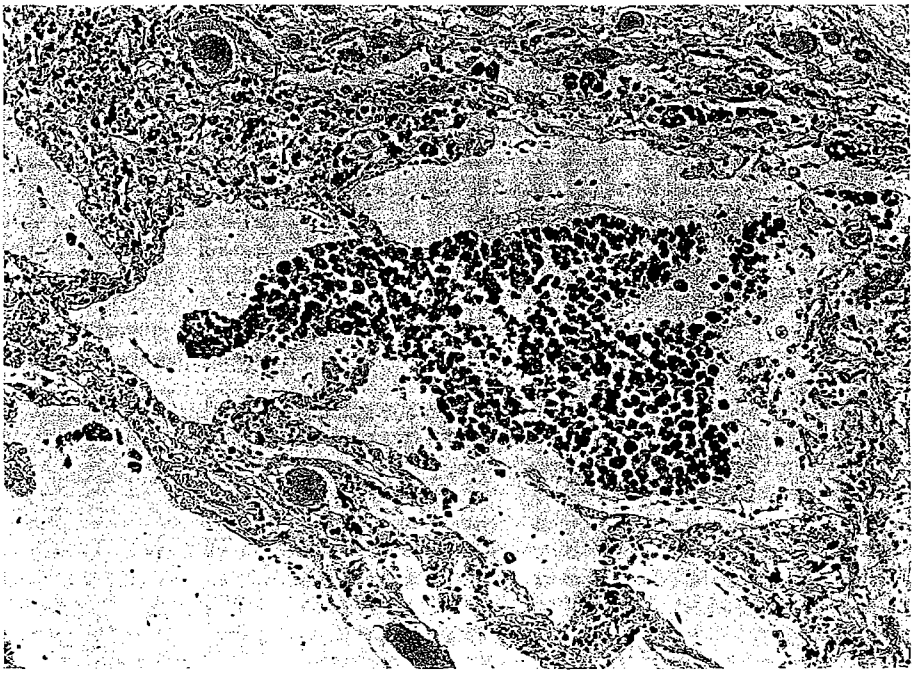

**Figure 60–56. Pulmonary Siderosis.** The section shows a large cluster of iron-containing macrophages within pulmonary air spaces. A smaller amount of iron is also present in the adjacent bronchiolar wall. Although there is some fibrosis in both airway wall and lung parenchyma, in this illustration, overall it was mild and present only focally. The patient was an electric arc welder who died accidentally. (×100.)

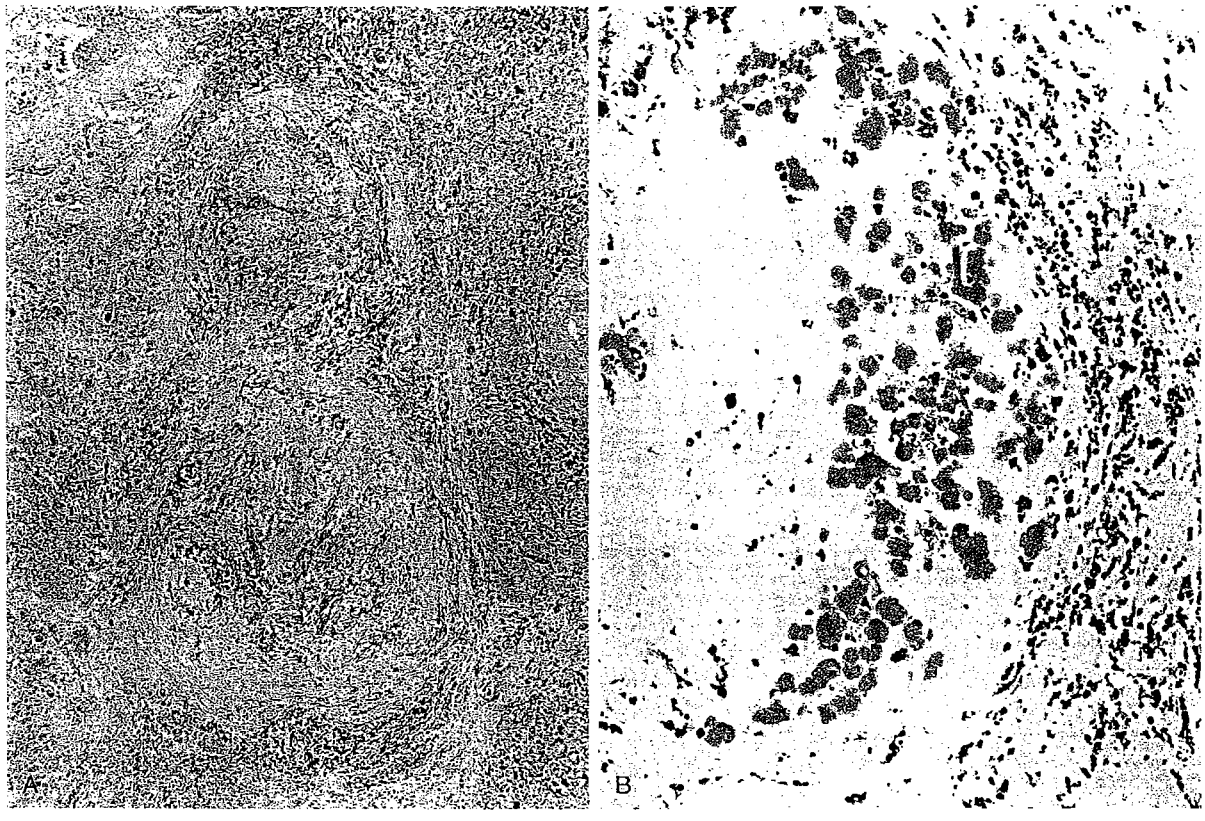


**Figure 60–57. Silicosiderosis.** A histologic section *(A)* from a 3-cm irregular mass in the upper lobe of a retired oxyacetylene torch welder shows extensive fibrosis with abundant interspersed pigment. Note the two rounded areas in the central portion that suggest that the mass was formed by confluence of multiple nodules. A magnified view of the pigmented material *(B)* shows it to consist of small black particles (predominantly anthracotic pigment) and larger, rather amorphous granules representing iron dioxide. (*A*, ×25; *B*, ×250.)

tion of 661 British electric arc welders, 7% showed small rounded opacities of 0/1 category or higher, there being a clear association between prevalence and years of exposure;[898] only 10 workers showed changes greater than 2/2. Opacities have been shown experimentally to correlate with localized aggregates of $Fe_2O_3$-laden macrophages[887] and are caused by the density of the $Fe_2O_3$ itself.[899] Individual shadows appear to be of lesser density than the nodules of silicosis. In contrast to the majority of cases of pneumoconiosis, the radiographic abnormalities can disappear partly or completely when patients are removed from dust exposure.[900] In silicosiderosis, the pattern depends somewhat on the concentration of free silica in the inhaled dust: When it is relatively low, the appearance is similar to that of pure siderosis or CWP;[16] when it is high, the pattern is identical to that of silicosis.[888]

Patients who have siderosis have no symptoms of chest disease; those who have siderosilicosis may complain of cough and dyspnea. In some patients, symptoms tend to be worse after the Monday work shift, suggesting that they are caused by fumes and vapors derived from the molding process. Even in the absence of radiographic abnormality, arc welders[901] and foundry workers[902] have been found to have a higher prevalence of bronchitis than control subjects. Pulmonary function studies of welders may show values considered to be within normal limits;[865] however, evidence of mild air-flow obstruction, even in nonsmokers, has been demonstrated by some investigators.[903–905]

The incidence of pulmonary carcinoma is significantly higher in patients who have siderosis or silicosiderosis than in the general population.[906–908] It is also higher in iron miners, although they are also exposed to other potential carcinogens.[909–911] In addition, squamous metaplasia, in many cases with atypical features, has been reported in a substantial number of iron foundry workers.[897] In one epidemiologic study in Scotland, higher standardized mortality rates for pulmonary carcinoma were grouped in residential areas most exposed to pollution from the foundries.[912] Despite these findings, there is no direct evidence linking $Fe_2O_3$ per se with the development of carcinoma.

### Iron and Silver

*Argyrosiderosis* results from the use of jeweler's rouge—which is composed in part of $Fe_2O_3$—as a polishing agent in the finishing of silver products. When it is applied with a buffer, small particles of $Fe_2O_3$ and silver are generated that may be inhaled. The radiographic manifestation in affected patients is rather characteristic, consisting of a fine stippled pattern in contrast to the reticulonodular pattern of siderosis. Pathologic examination shows the presence of

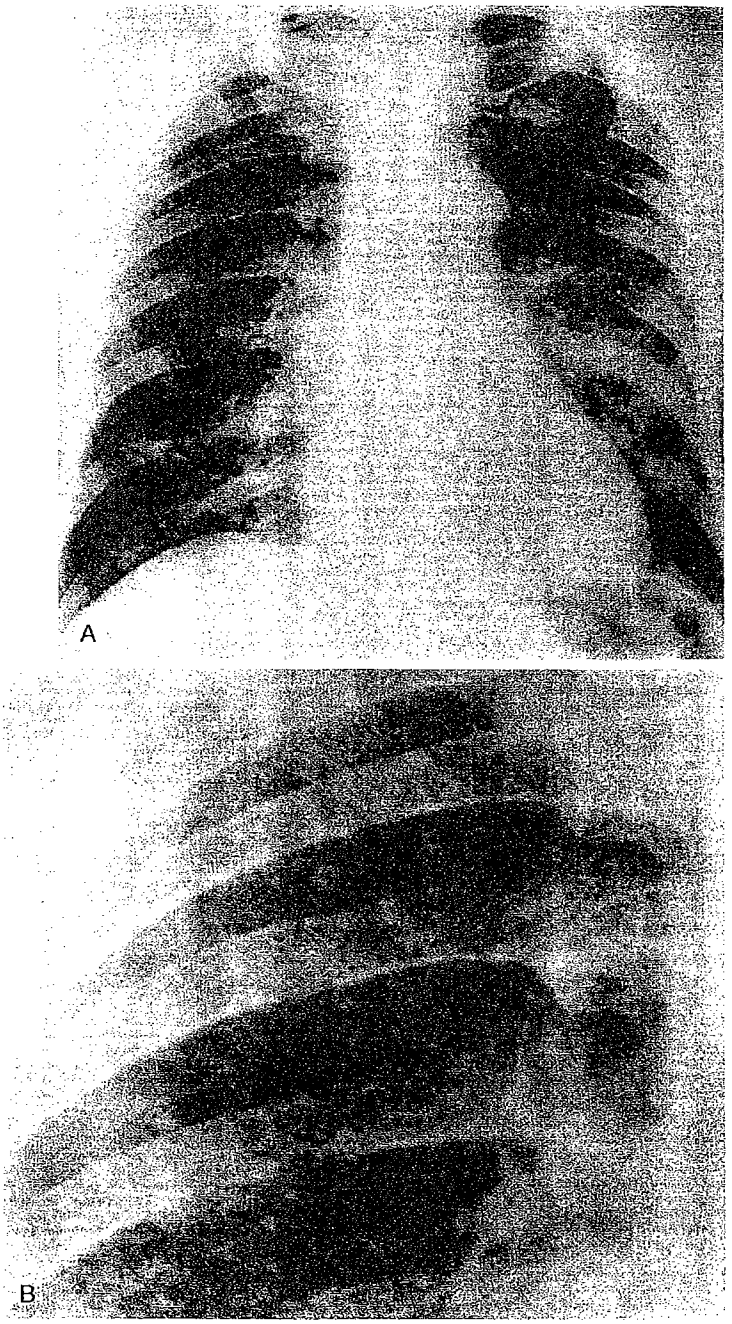


**Figure 60–58. Pulmonary Siderosis.** A 63-year-old man had worked as an electric arc welder for a railway company for 20 years. He was asymptomatic, this radiograph being part of a screening examination. Pulmonary function tests revealed lung volumes, ventilation, and diffusing capacity all to be in the low-normal range (the patient had been a heavy smoker for many years). The posteroanterior radiograph *(A)* and magnified view of the upper lung *(B)* reveal a diffuse reticulonodular pattern throughout both lungs, the opacities being of "low" density and thus rather poorly visualized. Hilar lymph nodes are not enlarged.

iron-laden macrophages in a distribution similar to that of pure siderosis; in addition, silver can be identified in the alveolar walls and the walls of small arteries and veins, particularly in relation to the internal elastic laminae.[913] Patients are typically asymptomatic.

### Tin

Pneumoconiosis caused by inhalation of tin (*stannosis*) occurs predominantly in individuals employed in the handling of the ore after it has been mined, especially in industries in which tin oxide fumes are created. Pathologic findings simulate the macule of CWP: Pigment-laden macrophages are found in alveoli, interlobular septa, and (most prominently) in aggregates adjacent to terminal bronchioles and proximal respiratory bronchioles; fibrosis is minimal or absent.[914] In contrast to CWP, focal emphysema is not a prominent feature.[914]

The high density of tin (atomic number 50) results in a dramatic radiographic appearance, consisting of multiple tiny shadows of high density, about 1 mm in diameter, distributed evenly throughout the lungs.[915] Linear opacities may be present in the paramediastinal zone, in the vicinity of the

diaphragm, and in the costophrenic angles. Lymph node enlargement has not been observed. A second pattern, seen chiefly in furnace workers in the tin ore industry, consists of larger, somewhat less numerous nodules.[916]

Even in the presence of significant radiographic abnormalities, clinical manifestations are typically absent. For example, in one study of 215 individuals exposed to tin oxide fumes, 95% of whom had worked in the environment for at least 3 years, 121 (56%) showed an abnormality on the chest radiograph;[915] none had symptoms or signs referable to the chest.

### Barium

Barium and its salts, particularly barium sulfate, have a wide variety of industrial uses as coloring or weighting agents, as fillers in numerous products, and in the manufacture of glass. Workers in many of these occupations as well as those who mine the ore can develop pulmonary disease (*baritosis*). Originally described in Italian workers,[888, 917] the abnormality has also been reported in the German,[918] French,[919] American,[920] and British[921] literature. Pulmonary disease caused by barium can also be seen after its aspiration or embolization in the hospital (*see* pages 2513 and 1865).

Radiographic abnormalities may develop after minimal exposure. As a result of the high radiopacity of barium (atomic number 56), the discrete shadows in the chest radiograph are extremely dense, creating an awesome appearance. The apices and bases usually are spared, and massive shadows do not occur.[921] The lesions characteristically regress after the patient is removed from the dust-filled environment.[888, 918, 921] Microscopic examination shows particles of barium in macrophages in air spaces and interstitial tissue, unassociated with fibrosis.

In one study of 118 Algerian workers exposed to dust containing a high content of barium sulfate, approximately 50% had abnormal chest radiographs.[919] Some of the affected individuals complained of chronic cough, expectoration, and asthma-like attacks; the degree of pulmonary function impairment was similar in those who had and who did not have radiographic abnormality.

### Antimony

Antimony is procured mainly from the mineral stibnite and is handled either as unrefined ore or as a fine white powder.[922] The main exposures are to antimony trioxide and, to a lesser extent, antimony pentoxide.[923] The substance is used in cosmetics; in the manufacture of batteries, pewter, printing type, and electrodes; in the compounding of rubber; in textiles, paints, and plastics as a flame retardant; and in ceramics as an opacifier.[922]

There has been little pathologic description of the effects of antimony on the lungs; in one brief report, dust-laden macrophages were identified in alveolar septa and perivascular tissue unaccompanied by fibrosis.[922] There is also experimental evidence confirming the lack of fibrogenic potential.[924]

The chest radiograph of affected individuals reveals minute dense opacities scattered widely throughout both lungs.[924] In one report of 51 workers exposed for at least 10 years to dust containing a high concentration of the mineral, radiographs were described as showing numerous *p* and occasional *q* opacities;[923] PMF was not seen. Respiratory symptoms were judged to be similar to those found in other pneumoconioses. Approximately 50% of workers had pustular skin lesions. There is no evidence that the dust causes significant disturbances in pulmonary function.

### Rare Earths

The rare earth elements include cerium (quantitatively the most important), scandium, yttrium, lanthanum, and 14 other minerals. Their atomic numbers range from 51 to 71, explaining the remarkable density of the radiographic shadows with which they may be associated. The elements are used in reactor control rods; in the manufacturing and polishing of colored glass; in the manufacture of flints; and as part of an alloy in cast iron, light metals, and heating conductors. Industrial exposure and reported cases of pneumoconiosis occur chiefly in workers in the graphic arts who are exposed to fumes from carbon arc lamps.[925]

There are few pathologic descriptions of the effects of rare earths on the lung. In animal experiments, they appear to be practically inert,[926] inducing only small collections of macrophages and, in one model of intratracheally administered lanthanum, an eosinophil response.[927] Some investigators, however, have described granulomatous inflammation and parenchymal fibrosis in exposed humans;[928, 929] there is evidence that the extent and progression of disease in these individuals depends to some extent on the thorium content of the dust.[928] As a result of these observations, earlier views that lanthanum causes benign pneumoconiosis only have been supplanted by the belief that it can result in pulmonary fibrosis, even in the absence of radioactive contaminants.[930]

The typical radiographic pattern consists of widely disseminated punctate opacities of great density, in one patient categorized as *q* opacities of 2/3 severity;[931] similar to some others described in the literature,[932] this patient was asymptomatic despite the spirometric demonstration of a restrictive impairment. Pulmonary "fibrosis" has also been described in some cases.[929]

## MISCELLANEOUS INORGANIC DUSTS

### Beryllium

Beryllium is a light, highly conductive mineral whose major commercial source is the aluminum silicate beryl, from which it is extracted at high temperature. Potentially important environmental exposure can occur to beryllium oxides during the extraction process and to a variety of beryllium alloys; beryl itself appears to be nontoxic.

Immediately before and during the 1940s, when its toxicity was first appreciated, the majority of cases of berylliosis resulted from exposure to beryllium in refineries, to beryllium alloys in metal working, and to fluorescent phosphor production for use in lamps. In 1949, dust control measures were introduced, which resulted in a dramatic decrease in the incidence of disease. It was not totally

eradicated, however, and many new cases have been reported since.[933] In a 1973 survey of workers in a beryllium extraction and processing plant that had been in operation for 14 years, 31 of 214 workers had radiographic changes compatible with interstitial disease;[934] it was determined that they had been exposed to dust concentrations well above the recommended level. It appears that beryllium sensitization does not occur in workers who are exposed to levels less than 0.01 $\mu g/m^3$;[935] however, it has occurred in workers exposed to a level of 0.9 $\mu g/m^3$,[936] a value that is well below the Occupational Safety and Health Administration safety standard of 2.0 $\mu g/m^3$.

The current major sources of exposure to beryllium have been outlined in reviews[937, 938] and include the processing and handling of beryllium compounds in the aerospace and electronics industry, the manufacture of gyroscopes and nuclear reactors,[939] the development of nuclear weapons,[940] the processing of ceramics, and the development or handling of beryllium metal alloys.[937, 941] Many components of automobiles and computers are composed of beryllium metal alloys;[937] disease has also been described in individuals involved in the manufacturing of dental prostheses.[942] Although significant exposure is still theoretically possible from breaking fluorescent lights, this is rarely seen today. Nonoccupational exposure causing disease has also been well described; it is invariably the chronic type (*see* farther on) and tends to occur in the household (e.g., a wife exposed to her husband's work clothes[943]) or in proximity to a site of beryllium use (e.g., secretaries and security guards working in a nuclear weapons facility).[939]

Berylliosis may occur in an acute or chronic form; as a result of improved industrial hygiene, the latter is now by far the more common.[938]

### *Acute Berylliosis*

The majority of patients affected with acute berylliosis have been exposed to a high level of dust, nowadays usually accidentally while working in beryllium refineries. Depending on the intensity of exposure, the clinical presentation may be either fulminating or insidious. In both situations, the pathologic changes are identical to those seen in other forms of acute chemical pneumonitis, consisting of bronchitis, bronchiolitis, and various stages of diffuse alveolar damage (interstitial and air-space edema, hyaline membranes, and fibrosis).[944, 945] Granulomatous inflammation does not occur.

The fulminating variety develops rapidly after an overwhelming exposure and may be rapidly fatal.[946] Clinical and radiographic manifestations are those of acute pulmonary edema.

The insidious variety produces symptoms weeks or even months after the initial exposure.[947] The onset is heralded by a dry cough, substernal pain, shortness of breath on exertion, anorexia, weakness, and weight loss. Auscultatory findings include crackles and, in some cases, wheezes suggestive of asthma.[948] Various nonpulmonary manifestations, including rhinitis, pharyngitis, conjunctivitis, and dermatitis, may occur with or without clinical and radiologic evidence of pulmonary involvement.[948] The chest radiograph usually does not become abnormal until 1 to 4 weeks after the onset of symptoms. Diffuse, symmetric, and bilateral "haziness" is seen in the earliest stage of the disease followed by the development of irregular patchy opacities scattered rather widely throughout the lungs. Subsequently, discrete or confluent mottling may be observed.[946, 948] Complete radiographic clearing may take 2 to 3 months.[948, 949] Pulmonary function studies have shown abnormal gas exchange at rest and on exercise, reduction in vital capacity, normal residual volume, and normal maximal breathing capacity (suggesting the absence of air-flow limitation).[947] Removal from exposure to the dust results in gradual return to normal function.

### *Chronic Berylliosis*

As indicated previously, chronic berylliosis is much more common than the acute variety and takes the form of a systemic granulomatous disease involving the lungs, pleura, lymph nodes, skin, and many visceral organs.

#### Pathogenesis

The frequent delay in onset of disease from the time of exposure, the decrease in beryllium content of the lungs of affected individuals with time (*see* farther on), the common presence of granulomatous inflammation, and the poor correlation between the degree of exposure and the development of disease all suggest that the pathogenesis of chronic berylliosis has an immunologic basis. Several specific clinical and experimental findings support this conclusion. Assuming an immunologic pathogenesis, it would be expected that the severity of exposure, including both dust and fume concentration, would not be a major factor in predicting the development of disease; reports of berylliosis associated with an air concentration of beryllium below the permissible exposure limit of 2 $\mu g/m^3$ appear to bear out this hypothesis.[941, 950] Cutaneous granulomatous inflammation develops in approximately 70% of affected patients on patch testing with a solution of beryllium sulfate. Similarly, blast transformation and the production of macrophage inhibition factor are common when lymphocytes of affected patients are cultured in the presence of beryllium.[951–955] This lymphocyte sensitization appears to be reversible with decreased beryllium exposure,[956] a finding that may be related to the reversibility of lung function abnormalities (*see* farther on).

Either by itself or acting as a hapten, beryllium appears to act as an antigen in invoking a delayed-type hypersensitivity response.[957] In this respect, the pathogenesis of berylliosis is remarkably similar to sarcoidosis, the disorder it imitates both clinically and pathologically. Pulmonary injury is an early event in the disease process. Markers of epithelial cell damage (e.g., serum KL-6) and alveolar-capillary permeability (e.g., BAL fluid/serum albumin) are elevated in patients who have chronic berylliosis and are able to distinguish between disease and sensitization.[958] The pattern of cytokine release from lymphocytes suggests that Th1 cells are activated after beryllium exposure;[959] levels of TNF-$\alpha$, IL-6,[960, 961] interferon-$\gamma$, and IL-2 are typically elevated, whereas those of IL-4 and IL-7 are not.[954, 962] The expansion of certain T-cell subsets in BAL fluid is also consistent with a local response to an antigen that includes beryllium.[894] Finally, levels of soluble TNF receptor I and II in serum and soluble IL-6 receptors and TNF receptor II in BAL fluid

correlate with pulmonary lymphocytosis and clinical measures of disease severity.[961]

A genetic marker for beryllium susceptibility has been identified in the HLA-DP allele in a position involved in susceptibility to autoimmune disorders. In one study, 97% of patients who had chronic berylliosis expressed the HLA-DPB1*0201 allele with glutamic acid present at residue 69, compared with only 30% of controls.[963] In another study of workers who were machining beryllium, 25% of those who were positive for this marker developed berylliosis compared with only 3.2% of those who were negative.[964]

### Pathologic Characteristics

The characteristic pulmonary abnormality in chronic berylliosis is interstitial pneumonitis,[945] which may have one or more of three histologic patterns: (1) a more or less diffuse mononuclear cell infiltrate unassociated with granulomatous inflammation (Fig. 60–59); (2) a similar infiltrate containing loose epithelioid cell aggregates and scattered multinucleated giant cells, frequently associated with calcified intracellular inclusions (Schaumann's bodies); or (3) well-formed, discrete, nonnecrotizing granulomas indistinguishable from those of sarcoidosis (*see* Fig. 60–59). Interstitial fibrosis is also common, occurring either diffusely within the parenchymal interstitium or in the form of well-defined nodules, often with central hyalinization, necrosis, or both.

In contrast to most other dusts that cause pneumoconiosis, beryllium is largely removed from the lungs with time and excreted in the urine (although it may be stored in bone and liver for many years); as a result, quantitative studies show significantly less tissue content of beryllium in chronic than in acute disease.[945] Despite this, the substance can be detected within affected tissues by laser probe and emission spectroscopy[965] and by laser ion mass analysis.[966] Measurements are most often made on tissue samples or urine, in which case there can be quantitative assessment; however, semiquantitative analysis can also be performed on frozen or formalin-fixed tissue sections.[967] Although there is overlap, in most patients the beryllium content of the lung and mediastinal lymph nodes is greater than that of normal individuals and of patients who have sarcoidosis.[968]

### Radiologic Manifestations

The radiographic pattern is neither specific nor diagnostic.[969] When the degree of involvement is relatively minor, the pattern has been described as a diffuse, finely granular "haziness" with a tendency to sparing of the apices and bases.[970] With more severe involvement, ill-defined nodules of moderate size are scattered diffusely throughout the lungs, sometimes associated with lymph node enlargement (Fig. 60–60). Calcification of nodules may occur.[971] In a group of 17 patients in whom the presence of chronic berylliosis was established by means of a positive lymphocyte proliferation

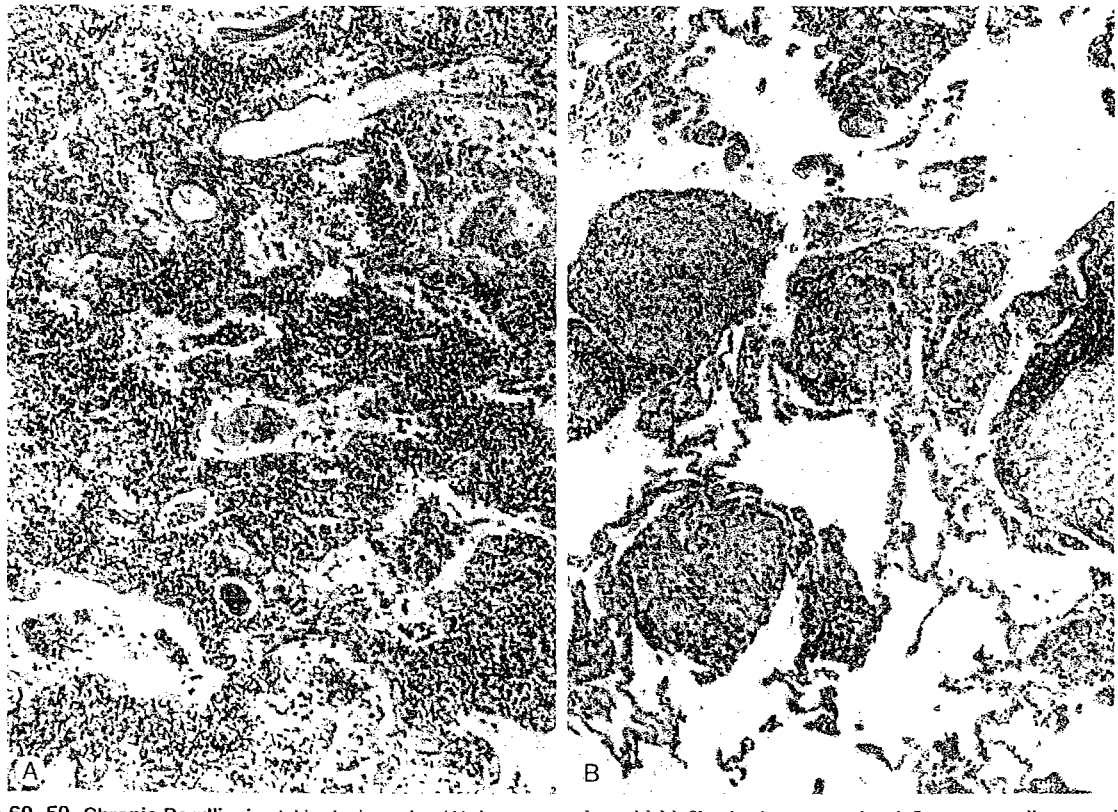


**Figure 60–59. Chronic Berylliosis.** A histologic section *(A)* shows severe interstitial infiltration by mononuclear inflammatory cells unassociated with granuloma formation. A different histologic pattern is shown in *B*, consisting of patchy, nonnecrotizing granulomatous inflammation within the pulmonary interstitium, similar to that seen in sarcoidosis. (From Freiman DG, Hardy HL: Beryllium disease. Hum Pathol 1:30, 1970.)

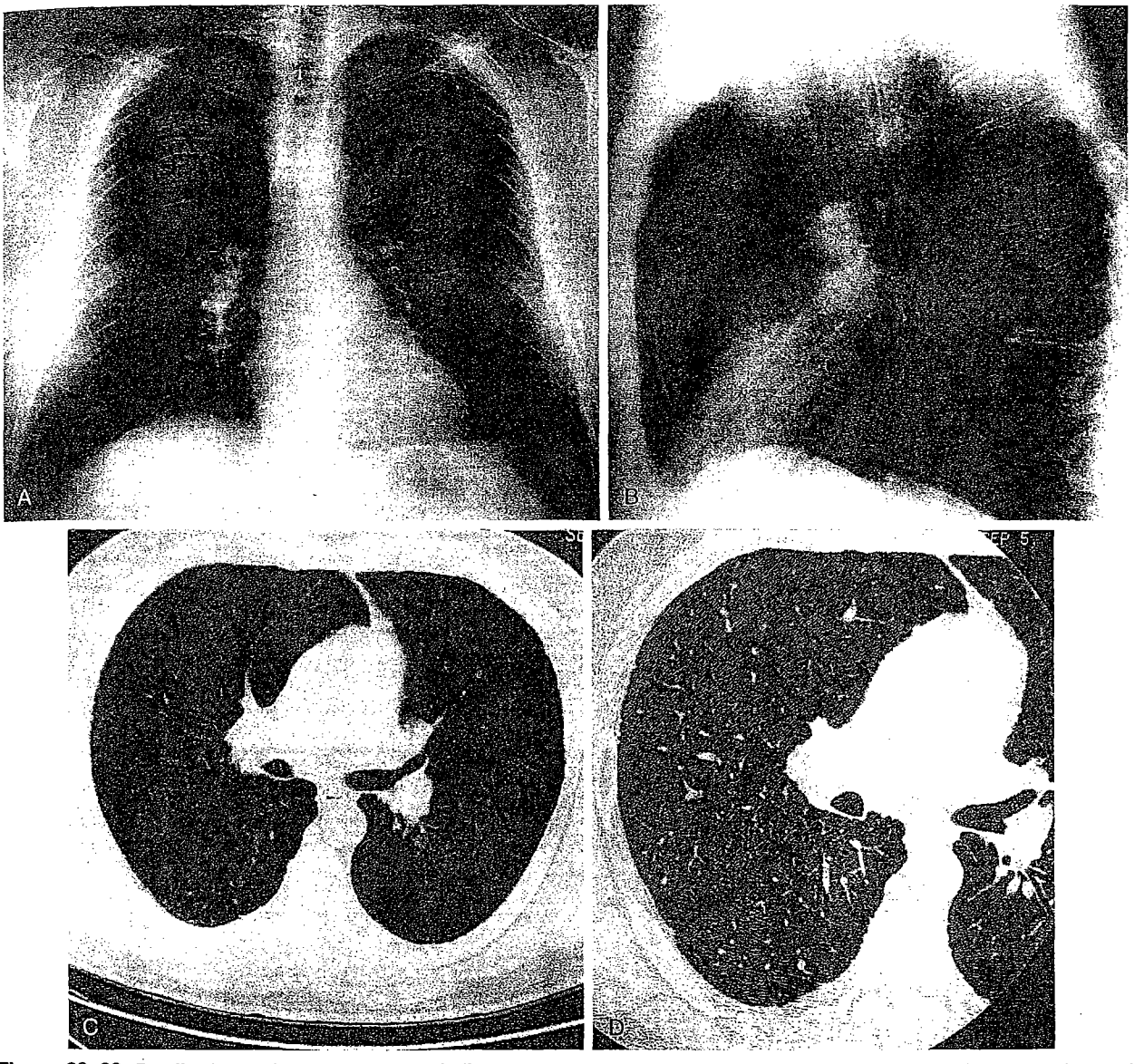


**Figure 60–60. Berylliosis: Radiographic and CT Findings.** Posteroanterior *(A)* and lateral *(B)* chest radiographs in a 46-year-old male ceramic plant worker show bilateral hilar adenopathy and fine nodules. The profuse fine nodules are confirmed on conventional CT *(C)* and HRCT *(D)* images. They are more evident on the 10-mm conventional CT image because more of them are contained within the imaging volume. The HRCT image, however, better demonstrates the tendency of the nodules to cluster along the visceral pleura, a distribution similar to that seen in patients with sarcoidosis. (Courtesy of Dr. David Lynch, University of Colorado Health Sciences Center, Denver, CO.)

test on BAL fluid, the most common radiographic abnormality consisted of diffuse, small, round and irregular opacities that involved all lung zones;[972] hilar node enlargement, linear scars, lung distortion, bullae, and pleural thickening were found less commonly. These changes did not correlate with pulmonary function abnormalities.

The findings on HRCT were compared with those on radiography in one study of 28 patients who had biopsy-proven disease.[973] Abnormalities related to beryllium were found in 21 (75%) patients by HRCT and in 15 (54%) by chest radiography. The most common findings seen with the former procedure were thickened interlobular septa and small nodular opacities (*see* Fig. 60–60). The nodules were well-defined and were seen mainly along the bronchovascular bundles or interlobular septa, a distribution similar to that in sarcoidosis.[974, 975] Other findings included pleural irregularities—presumably related to coalescence of subpleural nodules—in 7 (25%) patients and hilar or mediastinal lymph node enlargement in 11 (39%). Lymph node enlargement was seen only in patients who had an associated parenchymal abnormality.

In advanced cases, the pattern may be chiefly reticular and associated with a marked decrease in volume. CT scans in these patients demonstrate a predominantly reticular pattern frequently associated with honeycombing.[973, 976] Conglomeration of nodules may result in the formation of large